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THE EFFECTS OF INTRA-ABDOMINAL CARBON DIOXIDE INSUFFLATION IN THE PIGLET.

BY

ANDREW J. GRAHAM

A thesis submitted to the faculty of graduate studies and research in partial fulfillment of the requirements for the degree in **MASTER OF SCIENCE**

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

FALL, 1993

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ISBN 0-315-88041-4

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Dennis W. Jirsch

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ABSTRACT

Adult intra-abdominal surgery performed with minimal access surgery technique has created a revolution in surgery. This technique has remained largely unused for pediatric surgical procedures because of concerns regarding its safety and efficacy. At the present time intra-abdominal insufflation of CO_2 is the preliminary step to performing minimal access surgery. This study developed an animal model to determine the effects of intra-abdominal CO_2 insufflation in the infant. Eight piglets 4 -6 kg, 14 -19 days of age where instrumented under fentanyl anesthesia to allow measurement of arterial blood pressure (BP), central venous pressure (CVP), heart rate (HR), cardiac index (CI), inferior vena cava pressure (IVCp), inferior vena cava flow (IVCf), mediastinal pressure (Mp), partial pressure of CO_2 ($PaCO_2$), and minute ventilation (V_E) at baseline and during one hour of CO_2 insufflation to a pressure of 15 mmHg and again when ventilation was increased to control $PaCO_2$ levels. Continuous recording of data allowed time course analysis of 15 minute blocks to determine the rate of change of measured variables. A second group of 6 piglets 4-6 kg underwent the same instrumentation but had baseline values compared to those during N_2O insufflation to isolate the effects of increased intra-abdominal pressure.

During CO_2 insufflation alone the $PaCO_2$ increased by 31% ($p<.0001$). This increase in $PaCO_2$ ocurred within the first 15 minutes of insufflation and then remained stable. The increase in $PaCO_2$ was likely the result of increased CO_2 absorption from the peritoneal cavity as the V_E was unchanged

CO_2 insufflation alone was associated with a increase of 10% in CI ($p=.02$), 7% in SVR ($p=.04$), 17% in BP ($p<.0001$), 29% in CVP ($p=.01$) and no change in IVCf.

In contrast, when $PaCO_2$ was controlled by increased ventilation, there was no significant change in CI, a increase of 7% in SVR ($p=.02$), 57% in CVP ($p=.001$) and 7% in BP ($p=.01$), and a 22% decrease in IVCf ($p=.04$).

N_2O insufflation resulted in no significant change in CI, a increase of , 22% in SVR ($p=.01$), 35% in CVP ($p=.01$), 16% in BP ($p=.005$) and a 25% decrease in IVCf ($p=.02$).

CO_2 insufflation is associated with significant CO_2 absorption and increased myocardial work in the piglet model.

ACKNOWLEDGEMENTS

First, I wish to thank my supervisors, Dr. D. Jirsch, Dr. K. Barrington, Dr. N. Kneteman, and Dr. R. Rajotte. I am very grateful for their support and guidance throughout the project. I am particularly grateful for the time they took from their many responsibilities to be available for advice and discussion.

Secondly, I would like to thank Dr. M. Willerth for his generous assistance in the laboratory and Dr. A. Hayashi for suggesting this area of research.

I would also like to thank my parents for their unfailing support.

Special thanks to C. Olynyk for editing the manuscript.

Lastly, I wish to thank the Department of Surgery, University of Alberta and Linvatec for their financial support.

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LIST OF ABBREVIATIONS

minimal access surgery(MAS) 1

carbon dioxide(CO_2) 1

intra-abdominal pressure(IAP) 2

nitrous oxide (N_2O) 8

laparoscopic cholecystectomy(LC) 8

intra-abdominal pressure(IAP) 13

central venous pressure(CVP) 13

cardiac output(CO) 13

blood pressure(BP) 14

heart rate(HR) 14

cardiac index(CI) 14

partial pressure of carbon dioxide in arterial blood($PaCO_2$) 16

end-tidal CO_2(ET-CO_2) 16

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Chapter 1

INTRODUCTION

Intra-abdominal surgery has undergone a revolution in the last 5 years. Since the inception of intra-abdominal surgery access to the abdominal organs has been achieved via an incision in the abdominal wall to allow direct visualization and manipulation of the abdominal organs. The wound created in the abdominal wall requires closure which can be complex and time consuming. The wound itself is associated with complications such as infection, disruption, pain and cosmetic deformity. In 1987 Mouret performed the first laparoscopic cholecystectomy on a human, thus introducing a revolutionary approach to intra-abdominal surgery in which abdominal organs are visualized and manipulated under laparoscopic control via small abdominal wall incisions.[1]

Laparoscopic or minimal access surgery(MAS) allows visualization and manipulation of abdominal organs using different techniques than traditional or open surgery. MAS involves the placement of 3-5 trocars through the anterior wall into the peritoneal cavity. Visualization is achieved via the placement of an endoscope through one of the trocars. Manipulation of the organs is achieved with specifically designed instruments passed through the trocars. To allow safe passage of the trocars and to achieve adequate visualization requires elevation of the anterior abdominal wall from the abdominal organs. Elevation of the anterior abdominal wall is performed by insufflating carbon dioxide(CO_2) into the peritoneal cavity.

Cholecystectomy is the procedure most widely performed to date using MAS technique. Results to date have shown that patients who undergo

laparoscopic cholecystectomy have less post-operative pain, decreased length of hospitalization and more rapid return to regular activity.[2,3,4] The cosmetic results are excellent as four to five 1-1.5cm wounds are created. In the series reported to date this has been accomplished with a total complication rate of 1.6-5.1%.[3,4] For these reasons laparoscopic cholecystectomy has become the standard of care for symptomatic cholelithasis.[5] The excellent results achieved using MAS techniques for cholecystectomy have lead to its application in a large number of other procedures such as herniorraphy, fundoplication, appendectomy and colectomy.[6,7,8] Despite its wide spread use in adults MAS techniques have remained largely unused for infants undergoing intra-abdominal surgery as the result of fears regarding safety and efficacy. A small number of studies have reported on MAS used to perform cholecystectomy, pyloromyotomy and appendectomy in children.[9,10] These studies suggest that infants may benefit from MAS just as adults do.

The first step in the performance of MAS is to elevate the anterior abdominal wall from the abdominal organs. This is presently performed by insufflation of CO_2 into the peritoneal cavity to a pressure of 15 mmHg. Despite the favourable results reported for MAS, complications related to the insufflation of CO_2 have been documented. Hypercarbia, acidosis, arrhythmias, embolism and even cardiac arrest have been reported in adults.[11,12,13,14] The increased intra-abdominal pressure(IAP) as a result of the insufflation has been noted to alter hemodynamic variables in both human and animal studies.[15,16]

The effects of insufflation of CO_2 into the abdominal cavity in neonates and infants is largely unknown. Neonates and infants have an altered regulation of cardiac output and response to systemic acidosis; thus it is inappropriate to assume that results from adult studies can be extended to neonates and infants.[17]

The purpose of this study is to determine the hemodynamic and metabolic effects of CO_2 insufflation in the infant. Once the nature of the effects of CO_2 insufflation are known it may be possible to select those infants for whom the use of abdominal wall lifting devices other than insufflation of CO_2 is appropriate.

Chapter 2

MINIMAL ACCESS SURGERY

ORIGINS

The origins of MAS or laparoscopic surgery are found in the development of laparoscopy and endoscopy.

The initial motivation for the development of endoscopes was the desire to inspect the cavities of the human body. In fact the derivation of endoscope is from the Greek endo(within) plus the Greek skopein(to examine).[18] The invention of the endoscope is credited to Philipp Bozzini, who between 1803 and 1808 developed an endoscope which he called a lichtleiter or light conductor. This was followed by the development of the cystoscope by Salomon Segalas in 1826. During this same time period, John Fisher was the first to add an optical system to the simple hollow tube, appending a double convex lens to the endoscope to sharpen and enlarge the picture.[19] In the late 1800's, Nitze developed a cystoscope with multiple lenses within the tube, increasing the size of the visual field.[20] The resolution of these instruments was poor but was significantly improved upon by Hopkins, who developed the rod lens system. The design used by Hopkins was the reverse of that previously used in that he used glass rods to replace the air space and small air spaces to replace the former lenses. This system had the marked advantages of increased viewing angle, increased light transmission and improved resolution.[20]

A significant problem since the inception of endoscopy has been illumination. Bozzini's lichtleiter relied on a candle and a system of mirrors for illumination. Nitze initially used a distal illumination system with a small globe

at the tip of the instrument. This system was problematic as the globe was necesssarily small and its distal position allowed it to be easily covered with blood or secretions. To avoid these problems others have used a proximal light source and mirrors to aim light down channels dedicated to its transmission within the endoscope. This has the disadvantage of decreasing the size of the viewing port within the endoscope. A significant improvement came about with the use of rigid quartz rods which conducted light with minimal loss. It was Lamm's description, in the 1930's, of small flexible fiberglass fibers that would transmit light which heralded the development of the present day endoscope. The fibers were placed within the endoscope, surrounding the viewing quartz rod system. This is the system used widely in MAS. The fiberoptic system has now been adapted to allow image return as well as light conveyance and has resulted in the development of the flexible endoscope.[20]

The video endoscope encompasses the most recent development of the endoscope. The video endoscope does not use fiberoptic bundles for image transmission but rather has a charge coupling device at the tip of the instrument. This sensor transmits an image electronically to a video processor and the image is projected on a television monitor.

The history of laparoscopy is interwoven with the history of endoscopy. Laparo- is a combining form derived from the Greek lapara(flank) but it is used loosely in reference to the abdomen.[18] Thus a laparoscope has been defined as an instrument comparable to an endoscope by means of which the peritoneal cavity can be inspected.

The application of the endoscope to view the abdominal cavity was first reported in the early 1900's. Dimitri Oskarovich Ott, a Russian gynecologist, performed the first documented laparoscopy in 1901.[19] Georg Kelling of

Dresden, Germany reported the insertion of a cystoscope through the anterior abdominal wall of a dog, and he also developed a technique of insufflating filtered air into the peritoneal cavity.[21] Hans Christian Jacobaeus is credited with coining the term laparoscopy, reporting 45 cases of its use in 1910.[19] The first use of the laparoscope in the United States was reported by B.M. Berheim at Johns Hopkins University in 1911.[22]

The next significant advance occurred in the 1930's when Ruddock and Benedict became the main advocates of laparoscopy. Ruddock reported over 500 cases in which he used a laparoscope for diagnostic purposes or to perform tissue biopsy. [23]

The next 30 years saw laparoscopy develop in only a few centres. Perhaps the most notable of these was Kurt Semm of Kiel, Germany, a gynecologist and engineer who developed an automatic insufflation device.[23] In 1938 Janos Veres developed a needle for the creation of pneumothorax, later adapted to the creation of pneumoperitoneum and widely known as the Veres needle.[21]

It was not until the late 1960's and early 1970's that the laparoscope became widely used, predominantly by gynecologists. Berci and Gans were notable among the few general surgeons who used laparoscopy during this period. They reported its utility as a diagnostic technique in both adults and children as a diagnostic technique.[20,24]

In the 1980's the role of the laparoscope was expanded from that of simply diagnostic to operative. Semm reported the first laparoscopic appendectomy in 1983.[25] Laparoscopic cholecystectomy was performed on animals as early as 1972 but it was not until 1987 that Phillippe Mouret in Lyon, France performed the first laparoscopic cholecystectomy in humans.[26,1] In 1988 Dubois reported a series of patients whom had undergone laparoscopic cholecystectomy.[27] At the

same time in North America, Reddick widely promoted his technique of laparoscopic cholecystectomy using a laser.[28] Due to the remarkable response from general surgeons, 3 years later laparoscopic cholecystectomy was the procedure of choice for symptomatic cholelithiasis.[29]

FUNDAMENTALS OF MAS

The defining feature of MAS is the visualization and manipulation of intra-abdominal organs with instruments passed via trocars through the abdominal wall. The first step in MAS is the insufflation of CO_2 into the peritoneal cavity lifting the anterior abdominal wall away from the underlying intra-abdominal organs. Peritoneal insufflation of CO_2 can be accomplished in one of two ways. The first is a percutaneous technique in which a stylet, with a protective spring loaded sheath(Veres needle), is passed through the abdominal wall usually at the umbilicus. The stylet is then aspirated to ensure placement is not within a vessel or bowel lumen. If nothing is aspirated a saline drop test is performed, placing 3-5 drops of saline in the hub of the Veres needle and lifting the anterior abdominal wall. If the saline drops fall down the barrel of the Veres needle this suggests appropriate placement of the needle within the peritoneal cavity.

The second technique is an open one. An incision at the umbilicus is carried through the linea alba into the peritoneal cavity under direct vision. A trocar with a specifically designed flange(Hasson trocar) is placed in the incision allowing an air tight seal. Specific indications for the open technique are the suspected presence of adhesions, particularly in the upper abdomen.[30]

Once access to the peritoneal cavity has been achieved with the Veres needle or Hasson trocar, CO_2 is insufflated into the peritoneal cavity with observation of a pressure monitor to ensure that low intra-abdominal pressures

are maintained with a high flow rate of CO_2 indicating unimpeded gas flow. Insufflation is continued until an intra-abdominal pressure of 15mmHg is achieved. The benefits of using CO_2 include its rapid absorption (avoiding post operative abdominal distension), and the fact that it is not inflammable.[31] Nitrous oxide (N_2O) has been used in the past for diagnostic laparoscopy but since it can support combustion poses a theoretical and real risk if used in combination with electrocautery.[31]

After CO_2 insufflation, the Veres needle is removed and a 10mm trocar is inserted at the umbilicus. The presence of the CO_2 pneumoperitoneum should allow passage of the trocar without damage to intra-abdominal contents. The laparoscope is then passed through the trocar. The camera which is attached to the laparoscope is connected to the video monitor, thus allowing the surgical team to view the procedure. The pelvis and abdominal cavities are visualized and carefully reviewed to ensure no injury has occurred during insufflation. If an open technique has been employed, the laparoscope is inserted directly through the trocar at the completion of insufflation.

The nature of the intra-abdominal procedure to be performed dictates the placement of 3-5 additional trocars under the direct vision now provided by the laparoscope.[29,32]

RESULTS OF MAS

Cholecystectomy is the most widely performed and reported procedure using MAS techniques. The largest Canadian study to date reported on 2201 cases.[2]

The results of a recent open cholecystectomy study and those of the large laparoscopic cholecystectomy(LC) studies are shown in Table 1. LC has been associated with a marked decrease in length of hospital stay and in overall

complication rates. The time until return to full activity following LC is 11-12.8 days, a notable reduction from the 4-6 weeks usually required for return to full activity following open cholecystectomy.[33,3] The degree of post operative pain is reported to be significantly less following LC, as suggested by Peters et al who found that 70% of patients required only oral or no post operative narcotics.[33] The cosmetic results are superior, as only 4-5 incisions of 0.5-1.0cm are required. The rate of intra-operative conversion to open cholecystectomy is 3.6-4.7%.[3,4] In data reported from a single centre in the USA the mean cost of open cholecystectomy was slightly higher than LC ($4251.76 vs $3620.25).[33] It is for these reasons that laparoscopic cholecystectomy has become the procedure of choice for symptomatic cholelithiasis.[5]

The success of MAS to perform cholecystectomy has resulted in its application to a number of other procedures. Reports of laparoscopic, or laparoscopic assisted, colon resections have shown a shorter post operative ileus, less post operative pain and decreased hospital stay.[8,34] The list of procedures performed using MAS has expanded to include common bile duct exploration, truncal and selective vagotomy, and Nissen fundoplication.[35] Zucker has predicted that MAS will become one of the most common techniques used by general surgeons.[35]

COMPLICATIONS OF MAS

The complications of MAS can be divided into two broad groups. The first are those complications arising from the insufflation of CO_2. The placement of the Veres needle and trocars have been associated with major blood vessel disruption or damage to abdominal contents. The incidence of these injuries is 0.3%.[36] Intraperitoneal pressurized CO_2 is associated with a number of complications including hypercarbia, CO_2 embolus, subcutaneous emphysema,

arrhythmias, and even asystolic cardiac arrest.[37,11,13,38,14,12] Although such complications have been reported quite rarely.

The second group of complications are those related to the two dimensional view provided by the video monitors which can result in difficulties recognizing anatomical structures. The most common manifestation of this problem is identification of the comon bile duct during LC. Mistaking the common bile duct for the cystic duct has resulted in injuries to the common bile duct. The incidence of common bile duct injury is 0.14% to 0.5% during LC.[2,3,4]

Chapter 3

MINIMAL ACCESS SURGERY IN CHILDREN AND INFANTS

The role of MAS in children and infants is controversial. The earliest experiences occured in the 1970's when Gans and Berci performed diagnostic laparoscopy on children, a technique which was never widely adopted, probably due to the concurrent improvements in diagnostic imaging.[20] The later success of laparoscopic cholecystectomy in adults in the late 1980's led to its use in children. and LC in children as young as 5 years old has been performed in a number of centres.[39,10,40,41,42] Despite limited numbers, results have been uniformly excellent; children are usually discharged within two days of LC and return to normal activity within 5 - 8 days. No complications have been reported to date.

MAS techniques have been used to perform appendectomy. Gilchrist et al performed a prospective study comparing open and laparoscopic appendectomy in paediatric patients.[43] They were able to demonstrate a significant difference in inpatient days and time to return of full activity in favour of the laparoscopic approach. A single patient undergoing laparoscopic appendectomy developed a pelvic abscess related to a retained fecalith. Increased operative costs were also noted with laparoscopic appendectomy.

The assessment of impalpable testes and pylorotomy for pyloric stenosis have also been carried out laparoscopically.[44,9] In a report by Alain and colleagues the smallest patient to undergo an extramucosal pylorotomy was 2.63kg. No complications were reported in 10 patients who were hospitalized from 3-6 days post-operatively.

Despite these optimistic reports many paediatric surgeons feel that MAS will not be beneficial to paediatric patients. They argue that the advantages of laparoscopic surgery are offset by the disadvantages of increased operative time and an increased rate of complications. For example, they point out that a pyloromyotomy can be carried out through a very small incision in an open fashion, thus negating the advantages of a laparoscopic approach.

Other authors are pleased with the results to date and see the clear benefits of decreased post-operative pain and hospitalization provide by MAS.[45,46] Sackier notes that the decreased length of hospitalization results in a reduction of emotional stress a particularly advantage to young children.[46] A number of paediatric surgeons believe that one day most, if not all, neonatal and paediatric surgical procedures will be carried out via minimally invasive techniques.[45]

Chapter 4

EFFECTS OF INCREASED INTRA-ABDOMINAL PRESSURE

The effects of increased intra-abdominal pressure(IAP) are primarily hemodynamic.The hemodynamic effects of IAP have been studied in animals. Some of the earliest studies on this topic were performed by Booker.[47] In the 1940's he demonstrated the development of hypotension and eventual death in dogs who had a balloon insufflated within the peritoneal cavity. In the 1950's Guyton showed that femoral venous pressure was determined by IAP as long as the IAP was below the pressure within the thoracic vena cava.[48] He also showed that, at zero flow, the femoral venous pressure was equal to the IAP, but, as flow was increased, the femoral venous pressure climbed above the IAP. In 1976 Richardson and Trinkle found that sequential increases in IAP resulted in progressive decreases in central venous pressure(CVP), cardiac output(CO), and supra-diaphragmatic vena cava flow in adult mongrel dogs.[49] They also observed that no significant change in the blood pressure occurred during the sequential increase in IAP. The drop in CO was first noted at an IAP of 10 mmHg.

In 1981 Kashtan et al observed that an IAP of 40 mmHg created by intra-abdominal infusion of saline in dogs resulted in a decrease in CO but in distinction from Richardson and Trinkle, this was associated with an increase in right atrial pressure. .[15] They also point out that right atrial pressures are measured relative to atmospheric pressure, implying that increases in mediastinal pressure as well as transmural central venous pressure will alter the measured value for right atrial pressures. and that, accurate determination of

transmural venous pressure requires that mediastinal pressure must also be known. They also demonstrated that venous return was altered by the IAP. At increased intra-abdominal pressures the venous return was increased at right atrial pressures greater than 5mmHg and decreased at right atrial pressures less than 5 mmHg.

In 1972 Marshall et al measured the CO in 7 healthy young women aged 31-39 who had intra-peritoneal nitrous oxide insufflation at an unspecified pressure for approximately 8 mins. They found that the CO was significantly decreased and that blood pressure(BP) and heart rate(HR) were significantly increased.[16]

In 1974 Lynch et al studied the effects of IAP on 1 -3 day old piglets. Increased IAP was achieved by placing an inflatable rubber bag into the peritoneal cavity. A significant drop in the cardiac index(CI) occurred at IAP of 20 and 30 mmHg without a significant change in the pulmonary artery pressure.[50]

In 1992 Ryan et al examined the hemodynamic responses of peritoneal dialysis in three children following open heart surgery. They noted significant increases in right atrial pressure and mean pulmonary artery pressure but no significant changes in CI or systemic BP.[51]

To understand the possible effects of an increase in IAP the principles of hemodynamics must be understood. Flow through a blood vessel is determined by two factors: (1) the pressure difference at the two ends of the vessel, and (2) the resistance to blood flow. The resistance to flow is proportional to the viscosity of the blood and the length of the vessel. It is inversely proportional to the radius to a power of 4. These factors are combined in Poiseuille's law which yields the following equation.

$$Q = (\pi \Delta P r^4) / 8 \mu l$$

Where Q is flow, ΔP is the pressure gradient, r is radius, μ is blood viscosity and l is length.

Chapter 5

EFFECTS OF CARBON DIOXIDE IN THE PERITONEAL CAVITY

In the late 1960's both Baratz and Karis, and Alexander et al recognized that the insufflation of CO_2 into the peritoneal cavity would result in an increase in the partial pressure of carbon dioxide in arterial blood($PaCO_2$).[52,53] In 1970 Seed et al observed an increase in the end-tidal CO_2($ET\text{-}CO_2$) following insufflation of CO_2. These studies were all carried out on young healthy female patients with relatively short periods of CO_2 pneumoperitoneum (20-30 mins.). They concluded that CO_2 absorption does occur from the peritoneal cavity and they felt that the level of increased $PaCO_2$ was easily controlled with hyperventilation.[54] Significant increases in $PaCO_2$ during CO_2 pneumoperitoneum have also been demonstated in pigs and dogs .[55,56]

The time to a steady state of $PaCO_2$ during CO_2 insufflation has not been determined. Ho et al observed an increasing $PaCO_2$ in pigs at 1 hour of CO_2 insufflation at 15mmHg.[55]

In more recent work CO_2 insufflation has been associated with a greater degree of hypercarbia. Fitzgerald et al showed that dogs with papain induced lung damage had significantly increased CO_2 retention during CO_2 pneumoperitoneum.[11] They also demonstrated an increase in the $PaCO_2$ -$ET\text{-}CO_2$ gradient. Hypercarbia has also been noted during LC.[37] Wittgen et al demonstrated that patients undergoing LC with pre-existing cardiopulmonary disease had significantly elevated $PaCO_2$ above healthy controls.[57]

PHYSIOLOGY OF GAS EXCHANGE

Carbon dioxide absorption from the peritoneal cavity can be best understood by examining the problem of gas exchange in body cavities. Gas cavities within the body that are not ventilated can be divided into three groups. These are: 1)open non-ventilated, 2) closed rigid cavities, and 3) closed collapsible cavities. Closed collapsible cavities most closely model CO_2 pneumoperitoneum.[58]

The gas transport from such cavities occurs as the result of two sequential processes. The first is diffusion, which describes the movement of the gas from the cavity to the surrounding tissues. The rate at which diffusion occurs is dependent on a number of factors. If steady state is assumed the rate at which diffusion occurs is understood in terms of Fick's first law which states that the flux of gas is proportional to its partial pressure gradient. Also, the diffusion coefficient of the molecular species and its solubility coefficient in tissue directly affect the rate of diffusion. The product of these two coefficients is known as the permeation coefficient, and for CO_2 is 23-43 times higher than oxygen(O_2), implying that in a steady state that the equilibrium of the partial pressure of CO_2 in the cavity, tissue and blood will be achieved very rapidly. The surface area serving a capillary and the tissue thickness to reach the capillary are also directly proportional to the rate of diffusion.[58]

The second process that occurs is transport by the capillary of the gas. This is referred to as convection of the gas by the capillary away from the surrounding tissues. This is dependent upon the solubility coefficient of the gas in the capillary blood. The ability of blood to carry CO_2 is greater than its ability to carry oxygen. The ability of blood to carry CO_2 is affected by the presence of other gases such as O_2 which can in fact displace CO_2 . The rate of convection is

also dependent on the pressure difference of the gas in the surrounding tissue and that in the capillary blood. The last important factor is the rate of blood flow through the capillaries.[58]

Chapter 6

COMBINED EFFECTS OF INCREASED IAP AND CO_2 INSUFFLATION

The combined effects of increased IAP and CO_2 insufflation may be different from simply increased IAP. It has been proposed that hypercapnia may alter sympathetic discharge and thus alter hemodynamic responses.[55] Studies of the combined effects have been carried out in both animals and humans.

Ivankovich et al in 1975 studied the effects of CO_2 insufflated at an IAP of 40 mmHg in 15 dogs weighing 25-35 kg. The IAP was sequentially increased from 20 to 40 mmHg by 10 mmHg increments. Five minutes after each incremental change, measurements were taken. They observed an increase in $PaCO_2$ with increasing IAP. The CO was noted to decrease progressively, as was inferior vena cava flow(IVCf) as IAP increased. They also showed an increase in BP and right atrial pressure. However, when the right atrial transmural venous pressure was determined, this, in fact, decreased with increasing IAP. They also carried out insufflation with nitrous oxide and found similar hemodynamic changes but did not compare these directly.[56]

In 1992 Ho et al studied 8 pigs, 27-30kg, during laparoscopic cholecystectomy performed with CO_2 insufflation at 15 mmHg pressure. They observed changes in $PaCO_2$ and hemodynamic variables over a time period of 1 hour. The $PaCO_2$ was noted to steadily increase over the hour. They observed no change in CO or CVP but did note a decrease in the stroke volume.[55]

Studies performed to date in humans have been inconsistent. In 1972 Marshall et al studied 7 female patients between 21-38 years of age undergoing laparoscopic tubal diathermy. The patients received a general anesthetic but

breathed spontaneously. The IAP was 15-20 mmHg and each procedure lasted approximately 8 mins. CO was measured using a dye dilution technique and no change in CO was found but an increase in CVP and heart rate was observed.[16]

Kelman et al, in 1972, studied 39 female patients undergoing diagnostic laparoscopy for gynecological reasons. In this study the peritoneal cavity was insufflated to an IAP of 40 mmHg and then decrementally desufflated. Cardiac output was determined using indicator dilution techniques. They were able to note trends to an increase in CO at all levels of IAP but most dramatically at IAP less than 30 mmHg.[59]

In distinction to these findings, Lenz et al studied 24 patients during laparoscopic procedures using impedance cardiography. The IAP was not known, and the volume of gas insufflated was used as an end point for insufflation. Decreases in both CO and stroke volume were noted.[60]

In a recent study Westerband et al examined cardiovascular changes during laparoscopic cholecystectomy. During LC 16 patients had continuous monitoring of CO via impedance cardiography and BP, HR and ET-CO_2 were also recorded. LC was associated with a reduction in cardiac index of 30% and in HR of 5%. The BP increased by 15%. The calculated total peripheral resistance index increased by 79%. The authors speculated that decreased CO was due to a decreased venous return due to increased atrial filling pressure and inferior vena cava resistance. The authors suggest further that the increase in systemic resistance was an attempt to compensate for the decrease in cardiac output.[58]

Chapter 7

DIFFERENCES IN ADULT AND NEWBORN CARDIAC REGULATION

The effect of CO_2 insufflation may be different in the infant than the adult. The fetal & neonatal heart response to changes in preload, afterload and heart rate appear to be qualitatively similar to that of the adult, but with marked quantitative differences. These occur with reference to functional importance of the Starling relationship. For example, in the fetus and newborn(FN) an increase in atrial filling pressures from normal will result in little increase in CO. It is also notable that in the FN the right ventricular output is higher than the left. A possible explanation for this phenomena is that a maturational increase in myocardial compliance occurs.[17]

Another area in which a quantitative difference exists is in the response to changes in afterload. When shortening against the same load the immature myocardium shortens more slowly and by a smaller amount than does adult myocardium, implying that an adult would be able to eject against arterial pressure that would have a profound negative effect on fetal and neonatal function. This is thought to be particularly true for the right ventricle as increased afterload would result in increased wall tension.[17] This may have important implications as the IAP may lead to an increase in afterload.

The sympathetic nervous system also undergoes a process of maturation. In particular, changes occur in innervation, availability of neurotransmitters and number of adreno receptors. These take on increased significance when one realizes that in the FN the sympathetic nervous system plays a major role in adaptation of the cardiovascular system to challenges to homeostasis. This is

reflected in the ability of FN to tolerate the negative inotropic effects of acidosis as long as adrenergic support is available.[61] This may also be important in neonates and infants during MAS, as the CO_2 pneumoperitoneum may result in acidosis.

Chapter 8

CARBON DIOXIDE METABOLISM

Carbon dioxide metabolism has four components: production, transport, storage, and elimination. CO_2 is the end product of the oxidation of carbon containing substrates such as carbohydrates. The amount of CO_2 produced depends on the fuel source. When carbohydrates are utilized exclusively the amount of CO_2 produced exactly matches the amount of O_2 used. If lipids are used exclusively, CO_2 production is decreased by 30%.[62] Alterations in the production of CO_2 also occur as a result of changes in level of activity, fever, or disease. A temperature increase of 1°C above normal increases CO_2 production by 13%.[63]

The production of CO_2 occurs intracellularly resulting in a CO_2 pressure(PCO_2) of 46 mmHg. CO_2 diffuses very rapidly through the cell and into interstitial fluid such that the PCO_2 of interstitial fluid is 45 mmHg. The PCO_2 of the interstitial fluid is dependent on the production rate of CO_2 and blood flow so that an increase in the tissue flow will decrease the interstitial PCO_2 .

The transport of CO_2 in blood is the next step in the metabolism of CO_2 . In humans an average of 4ml of CO_2 is transported from the tissues to the lungs in each 100 ml of blood. CO_2 is transported in three forms in blood. The first is CO_2 in the dissolved state. In venous blood 2.7ml of CO_2 are found in 100ml of blood, this represents about 7% of all the CO_2 transported. The second form in which CO_2 is transported is as bicarbonate ion(HCO_3), the result of water(H_2O) and CO_2 combining to form carbonic acid. Within red blood cells this reaction is catalyzed by carbonic anhydrase an enzyme which increases the rate of reaction

5000 fold. This form of CO_2 makes up 70% of the CO_2 transported. The last form in which CO_2 is transported is carbaminohemoglobin, by a reversible reaction of CO_2 with hemoglobin, in a very loose bond. This comprises 23% of all CO_2 transported.[62]

Storage of CO_2 occurs in skeletal muscle and bone. The rate of reaction of CO_2 is slow taking weeks until equilibrium is reached with blood. Calcium carbonate is the form in which CO_2 is stored in bone .[64,54]

The elimination of CO_2 occurs in the lungs at the level of the alveoli. CO_2 rapidly diffuses from the blood across the pulmonary membrane to alveoli. The rate of elimination is controlled by the rate of blood flow and the alveolar ventilation.[62] The rate of blood flow is largely determined by CO, but, flow can be altered by certain noncardiac events such as pulmonary embolus which to some extent can be compensated for by increasing alveolar ventilation.

Alveolar ventilation is determined by total ventilation and also by the physiologic dead space. For example, total ventilation can be decreased by failure of the mechanics of breathing such as diaphragmatic paralysis and chest wall abnormalities. Intrinsic lung disease such as chronic obstructive lung disease results in an increased dead space. This results in an increase in CO_2 unless total ventilation can be increased to compensate.[63,62]

HYPERCAPNIA

The effects of hypercapnia are complex. The apparent complexity is probably the result of differences within species, age, type of anesthesia, duration and severity of hypercapnia. The most helpful approach is to note that the effects reflect a balance of largely stimulatory central effects and depressant effects on end organs. Superimposed upon this are the effects of anesthesia, age and species.[64]

AUTONOMIC EFFECTS OF HYPERCAPNIA

Increased sympathetic adrenergic activity occurs with hypercapnia. The increase in $PaCO_2$ is detected in two areas. The first is the aortic and carotid body chemoreceptors whose afferent stimuli are transmitted to respiratory and vasomotor centres. The second is a direct action of CO_2 on the respiratory and vasomotor centres, resulting in increased sympathetic nervous outflow and hyperventilation. Increased sympathetic activity can lead to an increased activity in the adrenal medulla with an increase in rate and force of cardiac contraction, and concomitant vasoconstriction. This response is not unlimited; as acidosis increases the sympathetically innervated cells are less able to respond.[65,64]

CIRCULATORY RESPONSES TO HYPERCAPNIA

The effect of hypercapnia on isolated cardiac muscle is decreased performance, as shown in a number of species including dogs, rabbits and guinea pigs, and appears to be mediated by a decrease in pH rather that a direct effect of CO_2. Peripherally, the direct action of CO_2 on blood vessels is relaxation for the majority of vessels with a notable exception in the pulmonary artery which undergoes vasoconstriction. The vessels most effected by CO_2 are capillaries and veins.[65]

Despite the negative effect on isolated cardiac muscle, cardiac output is generally increased in hypercapnia and has been attributed to increased contractility, decrease in afterload and hyperventilation.[66,65,64] This is not a completely consistent finding as Hansen et al have shown a decrease in CO in newborn piglets with hypercarbia.[67]

Chapter 9

SUMMARY

The introduction of MAS has revolutionized general surgery. This new and exciting technique is being tried for an ever expanding number of procedures including paediatric intra-abdominal surgery. A complete understanding of the technique is essential if this technique is to be safely used in paediatric intra-abdominal surgery. This requires an understanding of the effects of intra-abdominal CO_2 insufflation.

PURPOSE

The purpose of this study is to determine the effects of intra-abdominal CO_2 insufflation in a young animal model. Thus the effects of increased intra-abdominal pressure and the presence of high concentrations of CO_2 in the peritoneal cavity may be determined and understood.

HYPOTHESIS

1) The intra-abdominal insufflation of CO_2 alters hemodynamic parameters such as: cardiac output, inferior vena cava flow, femoral artery flow, central venous pressure, mean systemic pressure, inferior vena cava pressure, and heart rate.

2) The intra-abdominal insufflation of CO_2 alters $PaCO_2$.

3) The hemodynamic and metabolic changes that occur as a result of intra-abdominal CO_2 insufflation have a specific time course.

SIGNIFICANCE

An accurate understanding of the effects of intra-abdominal CO_2 insufflation in the piglet may predict the effects in infants. If an understanding of

these changes is achieved, appropriate intra-operative monitoring may be chosen for infants undergoing MAS. A better understanding of the effects of intra-abdominal CO_2 insufflation could determine a subset of patients for whom MAS utilizing CO_2 insufflation would be inappropriate.

Chapter 10

MATERIALS AND METHODS

ANIMAL MODEL

The extensive and invasive monitoring required to determine the effects of intra-abdominal CO_2 insufflation required an animal model. The piglet was chosen for a number of reasons. The morphological and functional characteristics of the pulmonary vascular bed of newborn piglets are similar to human neonates. Responses to septic shock and intravenous hyperalimentation closely mimic those observed in the human neonate.[68] Since the development of postnatal maturation of central nervous system regulation of cardiovascular function has been studied in piglets and the responses observed are physiologically similar to those observed in newborns, the piglet was chosen as an appropriate model for the human neonate.[69]

The piglets used were mixed strain , weighing from 4 - 6 kg. The age range was from 14 - 19 days.

SURGICAL PROCEDURE

Each animal was weighed then anesthetized with 5% halothane for induction, and 2% halothane for maintenance. Heart rate, respiratory rate, and rectal temperature were monitored continuously.

The right femoral vein was catheterized to 15 cm with a 5 Fr. umbilical artery catheter (Elecath, Eledro Catheter Corp. NJ) to monitor inferior vena cava pressure(IVCp) and to infuse fluids and medications. Normal saline was infused at 2.5x maintenance level (10 ml/kg/hr). Either the right or left femoral artery

was isolated and a 2 mm transonic flow probe (HT 207, Transonic Systems Inc., Ithaca, NY) was placed around the artery.

The right external jugular vein and common carotid artery were exposed and catheterized with 5 Fr. umbilical artery catheters to allow monitoring of CVP, systemic BP, and arterial blood gases. A tracheostomy was performed and the animal intubated with a 4.5 mm ID endotracheal tube (Sheridan Catheter Corp., Argyle, NY). Acepromazine maleate 0.2mg/kg, fentanyl 10µg/kg, and pancuronium bromide 100µg/kg were administered, halothane was discontinued and each animal was ventilated with a pressure cycled ventilator (Healthdyne 105, Marietta, GA) to achieve a partial pressure of oxygen (PaO_2) of greater than 80 mmHg and $PaCO_2$ of 35-45mmHg. Anesthesia was maintained with fentanyl 5µg/kg IV every 60 minutes. Paralysis was maintained with pancuronium bromide 100µg/kg every 30-60 minutes.

A median sternotomy was performed to allow the isolation of the main pulmonary artery and supra-diaphragmatic inferior vena cava. An 8 mm transonic flow probe was placed around the pulmonary artery and a 6 mm transonic flow probe was placed around the inferior vena cava. A fluid filled 5 Fr. umbilical artery catheter was then placed in the mediastinum to allow measurement of mediastinal pressure (Mp). The sternum was then reapproximated and the skin was closed.

A Veres needle was inserted supra-umbilically and placement of the tip in the peritoneal cavity was confirmed by the saline drop test. Insufflation of CO_2 or N_2O to a pressure of 15 mmHg was carried out by an automatic insufflator (Laproflator Electronic, Wiest & Fuchs, Germany).

Blood gases were analyzed with a blood gas machine (Instrumentation Laboratory 1306, Milano, Italy). Hemoglobin was determined with a Coulter counter (M430, Coulter, Hialeah, FL).

EXPERIMENTAL PROCEDURE

Following instrumentation a period of stabilization occurred during which ventilation was adjusted to ensure the $PaCO_2$ was 35-45 mmHg. Over a 15 minute interval baseline values were then recorded. The pulmonary artery flow, supra-diaphragmatic inferior vena cava flow, femoral artery flow, systemic, central venous, intra-abdominal inferior vena cava pressures, and heart rate were recorded continuously for 15 minutes with a Hewlett Packard 78342A monitor. Data was continuously acquired at a rate of 24 Hz with a 486/25 CPU (Dell Computer Corp. Austin, TX), using a data acquisition program written using the ASYST science\engineering package (ASYST Software Technologies, Inc., Rochester, NY) and was written by Aston Hugh, of the Royal Alexandra Hospital Neonatal Intensive Care Unit Research Department. Continuously acquired data were averaged and reported values reflect these averages. Arterial blood was sampled at the beginning and end of the baseline recording phase for arterial blood gas determination. The arterial blood gases were immediately analyzed and the reported values reflect the average of these two values. Minute ventilation (V_E) was determined using a thermostatic volume measurement device (Bear Medical Systems Inc. Riverside, CA)

During the second phase of the experiment CO_2 was insufflated to a pressure of 15 mmHg. Heart rate, blood flows, and pressure determinations were recorded in 15 minute blocks continuously for 1 hour. Arterial blood gases were sampled and analyzed every 15 minutes. to allow detection of any ongoing changes during the period of CO_2 insufflation.

During the third phase of the experiment CO_2 insufflation was stopped, the abdominal cavity desufflated and the rate of ventilation was increased by 5 breaths per minute. This typically increased the rate of ventilation from 13 bpm to 18 bpm. The heart rate, blood flows, and pressures were recorded for the initial 15 minutes of this phase. The arterial blood gases were sampled every 10 minutes to monitor elimination of excess CO_2 before a return to baseline conditions.

The fourth phase was a new baseline period during which no insufflation occurred and ventilation was returned to the same level as used in the initial baseline period. Heart rate, blood flows, and pressures were recorded continuously for 15 minutes and arterial blood gases were sampled at the conclusion of this time period.

The fifth phase was conducted with CO_2 insufflation to a pressure of 15 mmHg with an increase in V_E to match that of the value in the third phase. The heart rate, blood flows, and pressures were recorded in 15 minute blocks continuously for 1 hour. Arterial blood gases were sampled and analyzed every 15 minutes. This concluded the experiment and the animal was euthanized with pentobarbital 60 mg/kg IV.

A second set of experiments was conducted to examine the effects of insufflation of N_2O to a pressure of 15 mmHg. A baseline period of 15 minutes was recorded and arterial blood gases were sampled at the beginning and the end of the baseline period. The reported values reflect the average of these two values. Insufflation of N_2O was performed to a pressure of 15 mmHg. The minute ventilation was matched to that recorded during the baseline period by increasing ventilatory volumes or peak inspiratory pressure. The heart rate, blood flows, and pressures were recorded in 15 minute blocks continuously for 1

hour. Arterial blood gases were sampled and analyzed every 15 minutes. This concluded the experiment and the animal was euthanized with pentobarbital 60 mg/kg IV.

PHYSIOLOGIC MEASUREMENTS

The pulmonary artery, supra-diaphragmatic inferior vena cava, and femoral artery blood flows were measured with transonic flow probes. The pulmonary artery flow was used to represent the right ventricular output.

The central venous pressure, systemic blood pressure, inferior vena cava pressure, minute ventilation, mediastinal pressure and arterial blood gases were also determined during each experimental phase.

CALCULATED VALUES

The cardiac index was determined by dividing pulmonary artery flow by weight. The systemic vascular resistance was calculated by dividing the systemic blood pressure by the pulmonary artery flow. The inferior vena cava resistance (IVCR) was determined by dividing the difference of inferior vena cava pressure and central venous pressure by the inferior vena cava flow.

STATISTICAL METHODS

The following three experimental groups were studied.

Group 1: This group consisted of 8 piglets 14 - 19 days of age with an average weight of 4.8 kg (range 4 -6 kg). The baseline values were compared to the average values recorded for the 1 hour insufflation period using paired t-tests. A p value of less than 0.05 was considered significant. The average values recorded for baseline and each 15 minute period during insufflation were examined by an two factor ANOVA without replication. If the ANOVA detected a significant difference of $p < 0.05$ then a post hoc paired t-test was used to compare each 15

minute recording block to all others. This group is referred to in the text as the **CO_2 insufflation alone** group.

Group 2: This group consisted of the same 8 piglets as Group 1 who following a period of desufflation with hyperventilation had new baseline values recorded. The new baseline values were then compared to the average values recorded for the 1 hour of CO_2 insufflation with hyperventilation using paired t-tests. This group is referred to in the text as the **CO_2 insufflation with hyperventilation** group.

Group 3: The third group consisted of 6 different piglets 14 - 19 days of age with average weight of 4.5 kg (range 4-5 kg). The baseline values recorded were compared to those recorded during the 1 hour period of N_2O insufflation with paired t-tests. This group is referred to in the text as the **N_2O insufflation** group.

Chapter 11

RESULTS

Results obtained during baseline recording and those during insufflation for each experimental group are shown in Table 2.

PARTIAL PRESSURE OF CARBON DIOXIDE

A significant increase in the $PaCO_2$ occurred during CO_2 insufflation alone. No significant increase in $PaCO_2$ occurrred during CO_2 insufflation and hyperventilation. No significant changes in $PaCO_2$ occurred during N_2O insufflation.(Figure 1) The changes in $PaCO_2$ with time during CO_2 insufflation are shown in Figure 2. There was no significant difference in $PaCO_2$ values during the one hour insufflation period.

MINUTE VENTILATION

A small decrease in the minute ventilation occurred during CO_2 insufflation. This difference is not statistically significant. By design a significant increase in the minute volume occurred during CO_2 insufflation and hyperventilation. No significant change occurred during N_2O insufflation.(Figure 3). The minute ventilation determined at 15 minute intervals during the one hour of CO_2 insufflation did not differ significantly (Figure 4).

PARTIAL PRESSURE OF OXYGEN

A significant decrease in the PaO_2 occurred during CO_2 insufflation. No significant change occurred in the PaO_2 during CO_2 insufflation and hyperventilation. No significant change occurred during N_2O insufflation. (Figure 5)

SYSTEMIC MEAN ARTERIAL PRESSURE

A significant increase in BP occurred in all groups. (Figure 6) No significant changes in BP occurred within the one hour period of CO_2 insufflation. (Figure 7)

HEART RATE

No significant changes in heart rate occurred in any group. (Figure 8) The last 15 minute interval had a significantly higher heart rate than that recorded during the first 15 minutes of CO_2 insufflation. (Figure 9)

CARDIAC INDEX

A significant increase in cardiac index occurred during CO_2 insufflation but not during CO_2 insufflation with hyperventilation or N_2O insufflation. (Figure 10) No significant changes in cardiac index occurred within the one hour period of insufflation of CO_2 . (Figure 11)

CENTRAL VENOUS PRESSURE

A significant increase in central venous pressure occurred in all groups. (Figure 12) No significant changes in central venous pressure occurred within the one hour period of CO_2 insufflation. (Figure 13)

INFERIOR VENA CAVA PRESSURE

A significant increase in inferior vena cava pressure occurred in all groups. (Figure 14) No significant changes in inferior vena cava pressure occurred within the one hour period of CO_2 insufflation. (Figure 15)

INFERIOR VENA CAVA FLOW

The inferior vena cava flow decreased non-significantly during CO_2 insufflation alone. However, a significant decrease did occur during CO_2 insufflation with hyperventilation and N_2O insufflation. (Figure 16) No

significant changes in inferior vena cava flow occurred within the one hour period of CO_2 insufflation. (Figure 17)

INFERIOR VENA CAVA RESISTANCE

The resistance to flow in the inferior vena cava was significantly increased in all three experimental groups. (Table 2)

SYSTEMIC VASCULAR RESISTANCE

No significant changes in systemic vascular resistance occurred during CO_2 insufflation alone or CO_2 insufflation with hyperventilation. However, a significant increase did occur during N_2O insufflation. (Figure 18)

MEDIASTINAL PRESSURE

No significant changes in mediastinal pressure occurred during CO_2 insufflation alone or CO_2 insufflation with hyperventilation. However, a significant increase did occur during N_2O insufflation. (Figure 19)

FEMORAL FLOW

The femoral flow decreased in a non-significant manner during CO_2 insufflation alone. There were significant decreases in femoral flow during CO_2 insufflation with hyperventilation and N_2O insufflation. (Figure 20) No significant changes in femoral flow occurred within the one hour period of CO_2 insufflation. (Figure 21)

Chapter 12

DISCUSSION

CARBON DIOXIDE HOMEOSTASIS

A significant increase in $PaCO_2$ occurred during CO_2 insufflation. This increase in $PaCO_2$ was controlled by a corresponding increase in ventilation as demonstrated by the $PaCO_2$ in the CO_2 insufflation with hyperventilation group. (Figure 1) The rapid diffusion of CO_2 from pulmonary capillaries to alveolar gas results in the $PaCO_2$ being similar to the alveolar PCO_2 ($PACO_2$) with normal lungs.[70] The $PACO_2$ is in turn determined by the ratio of CO_2 production to alveolar ventilation. Alveolar ventilation(V_A) is the frequency of ventilation(f) multiplied by the difference between tidal volume(V_T) and volume of dead space(V_{DS}).

$$V_A = (V_T - V_{DS})\, f$$

There is no apparent reason to expect a significant increase in dead space volume during intra-abdominal CO_2 insufflation. Thus, in this model alveolar ventilation is proportional to frequency of ventilation multiplied by tidal volume, ie, minute volume. As demonstrated in Figure 3 a small non-significant decrease in minute ventilation occurs during CO_2 insufflation this suggests that the increase in $PaCO_2$ is due to an increase in production of CO_2 during CO_2 insufflation.

The production of CO_2 is determined by such factors as nutritional sources, temperature and presence of infection or malignancy. In this model the only variable with potential to have changed during the recording period is the temperature which is monitored continuously. The use of over head heating lights, warming blankets and servo heating control of the ventilator allowed the

maintenance of body temperature within a range of 38.5 - 39.0°C. Thus any change in the production of CO_2 between baseline and insufflation periods was likely due to CO_2 absorption.

Using the following equation:

$$PACO_2 \sim V_{CO_2} / V_A$$

If we substitute the minute ventilation volumes for alveolar ventilation and the $PaCO_2$ value for $PACO_2$ the CO_2 production(V_{CO_2}) is equivalent to 27.6 ml/min during baseline. The production of CO_2 during CO_2 insufflation alone is equivalent to 32.3 ml/min. The absolute values for CO_2 production here are clearly not accurate but do suggest that an increase in CO_2 production has occurred during CO_2 insufflation and this can only be explained by CO_2 absorption occuring.

Previous adult studies have suggested that absorption of CO_2 during insufflation is insignificant. Thus, it is important to attempt to explain this difference. As previously discussed the absorption of gas from semi-collapsible cavities is dependent on the pressure gradient, solubility of the gas, available surface area, thickness of tissue between the gas containing cavity and the capillaries, and the flow and density of capillaries.[58] The use of 100% CO_2 at a pressure of 15mmHg above atmospheric pressure results in a pressure gradient of approximately 650 mmHg, the same in both adults and infants. The solubility of CO_2 is high , 20- 30x that of O_2 but is clearly not altered between adults and infants. Unfortunately, no information about the peritoneal microcirculation is available for infants.[71] Studies examing the peritoneal suface have been reported in the nephrology literature and have shown that when compared to the adult, the neonate has twice as large a peritoneal surface per kg. However, the mean peritoneal surface area per m^2 is similar. Since neonates have a larger surface

area than adults.[71,72] The overall effect is that peritoneal dialysis is twice as efficient as that in adults.[71,72] This suggests that the increased absorption of CO_2 may have been the result of a larger surface area available for absorption.

Sampling of the arterial blood every 15 minutes during CO_2 insufflation allowed examination for change over this period. The results, as shown in Figure 2, revealed no significant change over the period of insufflation suggesting that changes in $PaCO_2$ occurred in less than 15 minutes.

Is this finding consistent with what is known about CO_2 metabolism? The time required for changes in CO_2 metabolism to reach equilibrium is determined by the rate of change of CO_2 levels in a number areas. CO_2 can be stored within the body in a number of reservoirs. It has been estimated that the human body can store up to approximately 120 litres of CO_2 . Storage of CO_2 occurs in alveolar gas, blood, muscle, visceral stores and bone.[64] CO_2 absorption occurs in the periphery (relative to the heart and lungs) the determination of the time to equilibrium is dependent on the time for peripheral stores to achieve equilibrium with central venous blood. Then a period of time is required for changes in central venous blood to be matched to those in the alveoli in which alterations in alveolar ventilation occur. An analysis of the points at which equilibrium must occur provides an understanding of the rate at which changes occur. The time required for diffusion of CO_2 from the peritoneal cavity to the microcirculation is likely to be very small because of the rapid diffusion of CO_2 . Equilibration of peripheral venous blood with that of central venous blood is dependent on cardiac output (ie. blood flow through peritoneal microcirculation). Figure 12 shows that any changes occurring in cardiac output in this experimental model do so within 15 minutes. Fahri and Rahn have observed that in the presence of a constant alveolar ventilation changes in cardiac output will result in changes in

$PACO_2$ that begin in one minute and reach their peak in a few minutes.[70] Thus , any changes in peripheral CO_2 could be equilibrated with those in the central venous blood in less than 15 minutes of insufflation.

The rate of readjustment between central venous blood and alveolar gases when alveolar ventilation is altered is exponential.[70] This suggests that the finding that alterations in $PaCO_2$ during CO_2 insufflation occurred in less than 15 minutes of insufflation is consistent with what is known about CO_2 stores.

As mentioned earlier CO_2 storage not only occurs in blood but also muscle, viscera, and bone; the changes occurring in blood do so on the order of minutes. In this animal model however an increase in $PaCO_2$ lasts for 1 hour in the CO_2 insufflation alone group. It is believed that any changes in bone CO_2 stores require an elevation of the mixed venous CO_2 for several weeks before a significant difference is noted. It is felt however, that changes in muscle and visceral stores may occur if elevation in mixed venous CO_2 is present for periods of 20-60 minutes.[54] If this is occuring in this model it is not occuring to a large enough extent to decrease the $PaCO_2$ within the 1 hour insufflation period.

OXYGEN HOMEOSTASIS

A significant decrease in PaO_2 occurs during CO_2 insufflation. (Figure 5) This decrease in PaO_2 is not evident during CO_2 insufflation and hyperventilation. The gas law states that:

$$PV=nRT$$

In this equation P is the pressure, V is volume, n the number of moles of gas, R is the gas constant and T is the temperature. Dalton's law states that the total pressure of a mixture of gases is equal to the sum of the partial pressures of each gas in the mixture.

$$P_{total} = p_A + p_B + p_C + \cdots$$

In the research model the P_{total} remains constant at atmospheric pressure during end expiration as continuous positive pressure ventilation was not used. Since the $PaCO_2$ has increased, the gas law implies that an increase in volume must occur. Thus, the gas equation as it applys to oxygen alone indicates that since the volume has increased but the number of moles of oxygen, gas constant, and temperature have not changed, then the PO_2 in the alveolus must decrease and therefore the PaO_2 in turn.

HEMODYNAMICS

A significant increase in the IVC pressure occurred in all groups. (Figure 14) This increase was independent of the type of gas insufflated since it occured with the insufflation of CO_2 or N_2O. IVC pressure increase also occursred independently of $PaCO_2$ levels as it was observed during CO_2 insufflation and CO_2 insufflation with hyperventilation. This suggests that the increase in IVC pressure was the result of the increased intra-abdominal pressure.

This may be explained in the following manner. The pressue monitors are zeroed to atmospheric pressure thus measured pressure in the IVC is relative to atmospheric pressure. An increase in pressure implies an increase in force over a given area. The increase in intra-abdominal pressure created by the insufflation increases the force over the largely unchanged area of the peritoneal cavity. To bring about an increase in measured pressure this force must be transmitted to the blood within the vessel. The fact that the IVC pressure is increased indicates that IVC compliance is high.

The detected increase in the IVC pressure is approximately 10 mmHg. It is worthwhile noting that the IVC pressure is not simply equal to intra-abdominal pressure nor to the sum of baseline IVC pressure and intra-abdominal pressure.

Noting that:

IVC pressure = IVC transmural pressure + IAP

Since the IVCp increased less than the intra-abdominal pressure the IVC transmural pressure must have decreased. This implies that IVC volume has decreased due to IVC compression.

CENTRAL VENOUS PRESSURE

A significant increase in the CVP occurred in all three experimental conditions.(Figure 12) This suggests that this change was a result of increased intra-abdominal pressure and not the result of CO_2 absorption.

An increase in the measured CVP could reflect changes in the atrial transmural pressure or the mediastinal pressure or a combination of both as shown for inferior vena cava pressure. An increase in intra-abdominal pressure will result in an elevation of the diaphragm in a paralyzed animal. An increase in the mediastinal pressure is the potential result. It was important therefore to measure the mediastinal pressure impacting on the central veins. (Figure 19) No significant change of the mediastinal pressure occurred during insufflation in the CO_2 insufflation group and CO_2 insufflation with hyperventilation group. There was however, a significant increase in the mediastinal pressure in the N_2O insufflation group, was likely due to the method used to match the minute volumes received during baseline and that received during insufflation of N_2O. To match these volumes during N_2O insufflation the flows and peak inspiratory pressures were increased, leading to an increased trans-thoracic pressure. This did not occur in the CO_2 insufflation and hyperventilation group as the increased ventilation was achieved via an increased respiratory rate. The CVP data for the N_2O insufflation must be viewed within this context.

The analysis of mediastinal pressure suggests that it was not the significant factor in understanding the increasing the CVP during increased

intra-abdominal pressure. The increased CVP is therefore due to an increase in central venous transmural pressure, probably due to increased right atrial blood volume.

INFERIOR VENA CAVA FLOW

Venous return is determined by the difference of central venous pressure and peripheral venous pressure. It has been shown that during insufflation both the CVP and inferior vena cava pressure are increased. It is accordingly difficult to predict changes in venous return from that portion of the body drained by the inferior vena cava. The measurement of the supra-diaphragmatic inferior vena cava flow directly allowed us to determine this value. Figure 16 shows that significant decreases in inferior vena cava flow occured during CO_2 insufflation with hyperventilation and during N_2O insufflation. A non-significant decrease occurred during CO_2 insufflation alone. Recall:

$$R = \Delta P / Q$$

This allows one to determine the resistance to flow in the inferior vena cava. The resistance to flow is significantly increased during insufflation in all 3 groups.

Resistance is determined by a number of factors which are shown in the following equation:

$$R = 8 \mu l / \pi r^4$$

Thus, resistance is directly proportional to viscosity (μ), length (l) and inversely proportional to the fourth power of the radius (r). It is unlikely that insufflation altered the viscosity of the blood or the length of the inferior vena cava, therefore changes must have occurred in the radius of the vessel; these could have been due to increased external pressure or alterated sympathetic tone and venoconstriction. Increased sympathetic tone could have also been due to stretching of the peritoneum.

HEART RATE

The heart rate was not significantly changed in any of the three experimental groups.(Figure 8) The autonomic nervous system and degree of the right atrial stretch are important factors in determining heart rate.[62] This experimental model does not allow for any firm conclusions as to which of these is the predominant factor in heart rate control. It would seem that stimuli to the sympathetic nervous system, such as changes in $PaCO_2$, surgical stress, level of anesthesia, and blood pressure would be preeminent in this model. Whatever stimuli were operative; there was minimal change in heart rate during intra-abdominal insufflation.

SYSTEMIC VASCULAR RESISTANCE

Systemic vascular resistance was significantly increased during CO_2 insufflation with hyperventilation and during N_2O insufflation. Systemic vascular resistance was not however altered during CO_2 insufflation alone. (Figure 18) Systemic vascular resistance is a calculated value which reflects the resistance to flow from the root of the aorta to the right atrium. In the normal physiologic setting the greatest resistance to flow is found at the level of the arterioles.[73] As indicated previously the resistance to flow is dependent primarily on radius. As previously discussed resistance to flow increased in the inferior vena cava. However it is likely that an increase resistance to flow was also present in the splanchnic arterioles. The increased resistance to flow likely represented a combination of these effects.

In CO_2 insufflation alone group no change in sytemic vascular resistance was detected despite significant increase in IVC resistance to flow. This suggests that a decrease in resistance to flow must have occurred in the arterial circuit likely mediated via an increased $PaCO_2$.

CARDIAC INDEX

The cardiac index was significantly increased during CO_2 insufflation alone but not during CO_2 insufflation with hyperventilation and N_2O insufflation. (Figure 10) The increase in cardiac index which occurred during CO_2 insufflation alone was evident in the first 15 minutes and was maintained throughout the one hour insufflation period. No significant changes in cardiac index occurred during the period of insufflation suggesting that the hemodynamic changes took place over a time frame of 10 -15 minutes and then were maintained.

The cardiac index is determined by the stroke volume and heart rate.

$$CI = CO/\text{wt. in kg} = (SV * HR) /\text{wt. in kg}$$

This is shown in the above equation where cardiac index is CI, cardiac output is CO, stroke volume is SV, and heart rate is HR. Since no significant changes in heart rate were present, any changes in cardiac index were likely to reflect changes in stroke volume.

The stroke volume is determined by preload, afterload, and contractility. Cardiac Index is equal to venous return. The venous return is a measure of the volume of blood delivered to the right atrium and is determined by the pressure differential between the central venous pressure and the peripheral venous pressure.[74] Discussed above was that the portion of venous return contributed by the inferior vena cava was measured by inferior vena cava flow. In the case of CO_2 insufflation alone the inferior vena cava flow was decreased slightly by a nonsignificant amount. Thus, alteration in cardiac index cannot be accounted for by changes in inferior vena cava flow during CO_2 insufflation alone. Similarly, during CO_2 insufflation with hyperventilation and N_2O insufflation, no significant changes occurred in the cardiac index despite significant decreases in

inferior vena cava flow. Again suggesting that factors other than inferior vena cava flow play a significant role in determining cardiac index.

A second important finding was shown by the changes in cardiac index and inferior vena cava flow that occur during all three experimental groups. Venous return must equal the cardiac output eventually as the circulatory system is essentially a closed one any difference between venous return and cardiac output must be a transient one.[73] Since IVC flow has decreased but cardiac index has been unchanged or increased a redistribution of cardiac output must have occurred. A proportional decrease in blood flow to that part of the body drained by the inferior vena cava has occurred in all experimental groups. This change, present in all three groups, suggests that the alteration in distribution of cardiac output was the result of increased intra-abdominal pressure. The corollary of decreased flow to the lower portion of the body is that increased flow must be distributed to the head and upper limbs.

The afterload as measured by systemic vascular resistance during CO_2 insufflation alone was not changed. The cardiac index was increased in this experiment despite the lack of a decrease in systemic vascular resistance that would be expected if this were to account for the changes in cardiac index. In the CO_2 insufflation with hyperventilation and N_2O insufflation groups significant increases in systemic vascular resistance was present. No significant changes, however, were detected in cardiac index. Once again, this suggests that afterload changes are not playing a central role in regulation of cardiac index during insufflation. The increased systemic vascular resistance may however, play a central role in bringing about the redistribution of cardiac output.

Changes in cardiac index are unlikely to be the result of alterations in heart rate or afterload. This suggests that changes in myocardial contractility

may be playing an important role in determining the new setpoint of cardiac index during insufflation. In the CO_2 insufflation alone group a significant increase in cardiac index has occurred. Recall that this is also the group in which a significant increase in $PaCO_2$ is present. Prys-Roberts has noted that an increase in $PaCO_2$ can cause a significant increase in cardiac output in 1 year old lambs.[64] Hansen et al however, noted no significant change in cardiac output with an increase in $PaCO_2$ in 1- 4 day old piglets.[67] However, nitrous oxide anesthesia was used in Hansen et al study which is likely to be more cardioactive than the fentanyl used in these experiments. As discussed previously $PaCO_2$ effects are mediated through sympathetic pathways. Thus the increased cardiac index detected in this experiment may be the result of increased myocardial contractility secondary to sympathetic stimulation from an increase in $PaCO_2$. An alternate source of sympathetic stimulus may be the stretching of the peritoneum.

SYSTEMIC BLOOD PRESSURE

The systemic blood pressure was significantly increased in all experimental groups. (Figure 6) This finding suggests that the increase in blood pressure can be attributed to increased intra-abdominal pressure. However, this may not be the case. Blood pressure is determined by cardiac output and resistance. In the case of CO_2 insufflation alone the predominant mechanism in increased blood pressure is increased cardiac output as the systemic vascular resistance is unchanged. In the CO_2 insufflation with hyperventilation and N_2O insufflation groups the cardiac output was not significantly changed, and the systemic vascular resistance was increased. This suggests that the systemic blood pressure was determined by the complex interaction of the effects of increased $PaCO_2$, changes in cardiac output and systemic vascular resistance.

FEMORAL FLOW

The femoral flow was not significantly changed during CO_2 insufflation alone but was significantly decreased during CO_2 insufflation with hyperventilation and N_2O insufflation. The validity of the data may be questioned here as often the femoral artery flow was measured from the same limb in which the femoral vein had been ligated. This data suggests that significant decreases in femoral flow may occur. The changes may reflect changes in the redistribution of blood flow and alterations in resistance to flow.

Chapter 13

CONCLUSIONS

The piglet is a reasonable model of the infant for examining the physiologic changes that occur with intra abdominal CO_2 insufflation. CO_2 insufflation of the peritoneal cavity to a pressure of 15 mmHg is associated with significant increase in $PaCO_2$ as the result of absorption of CO_2 from the peritoneal cavity. The $PaCO_2$ levels can be controlled by an increase in the rate of ventilation. CO_2 insufflation is associated with significant increases in central venous pressure, inferior vena cava pressure and systemic arterial pressure. Alterations in cardiac output during CO_2 insufflation reflect changes in myocardial contractility and the cardiac output is maintained or increased despite decreases in inferior vena cava flow. The hemodynamic changes seen during CO_2 insufflation in the piglet reflect a balance of the effects of $PaCO_2$ and increased intra-abdominal pressure altering resistance to flow and myocardial contractility. These findings contribute to a greater understanding of the physiologic changes occurring during intra-abdominal CO_2 insufflation.

As a result of this study we recommend the following: 1) intra-abdominal CO_2 insufflation to a pressure of 15 mmHg is likely to be safe in healthy infants; 2) any infant undergoing intra-abdominal CO_2 insufflation have the $PaCO_2$ levels monitored closely intra-operatively; 3) infants that do not have the increased pulmonary reserve to tolerate the increase in ventilation required to maintain $PaCO_2$ levels in the normal range during CO_2 insufflation should be considered for minimal access surgery techniques using alternate abdominal wall lifting devices or traditional open surgery; 4) infants lacking the myocardial reserve to

tolerate increased central venous pressures, increased systemic vascular resistance or myocardial work also be considered for minimal access surgery techniques using alternate abdominal wall lifting devices or traditional open surgery.

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TABLE 1

Study	Hospital Stay(days)	All Complications %	Bile Duct Injuries %
Open Cholecystectomy [5]	6-9	12-14	0.0
Southern Surgeons[4]	1.2	5.1	0.5
European[3]	3	1.6	0.3
Peters et al[33]	1.1	8	1.0

TABLE 2

	Baseline	post-IACI	New Baseline	post-IACI+V	N_2O Baseline	N_2O Insufflation
CI (ml/min/kg)	136±33	158±42*	138±32	138±38	151±22	147±11
IVCf (ml/min)	480±157	452±194	503±162	394±105†	403±59	304±66‡
BP (mmHg)	65±13	76±12*	73±14	78±14†	75±12	87±11‡
CVP (mmHg)	6.8±2.6	8.8±3.0*	7±3	11±3†	5.4±1.9	7.3±2.9‡
IVCp (mmHg)	14±3.9	27.7±6.9*	15±4	25±4†	8.8±2.2	20±3.2‡
HR (bpm)	175±32	184±29	193±36	195±30	184±29	198±20
$PaCO_2$ (mmHg)	36.85±3.29	48.26±4.83*	36.4±4.3	37.4±4.1	39.1±3.9	42.1±4.5
PaO_2 (mmHg)	167±51	141±54*	140±52	125±34	149±43	150±34
V_E (L)	0.75±0.12	0.67±0.12	0.8±0.2	1.1±0.2†	0.90±0.27	0.83±0.18
Mp (mmHg)	4.8±2.5	5.2±2.4	4.8±2.9	5.5±2.3	3.8±1.8	5.8±1.2‡
SVR(mmHg/ml /min/kg)	0.50±.14	0.51±.14	0.55±.14	0.59±.15†	0.49±.08	0.60±.09‡
IVCR(mmHg/ml /min/kg)	0.017±.01	0.058±.03*	0.019±.01	0.041±.02†	0.009±.005	0.045±.01‡

* † ‡ indicate $p<.05$ for paired t-test comparing baseline and post insufflation values

Baseline and Post-Insufflation values for: intra-abdominal CO_2 insufflation (IACI) alone, intra-abdominal CO_2 insufflation and hyperventilation (IACI + V), and N_2O insufflation.

FIGURE 1

$PaCO_2$ levels at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

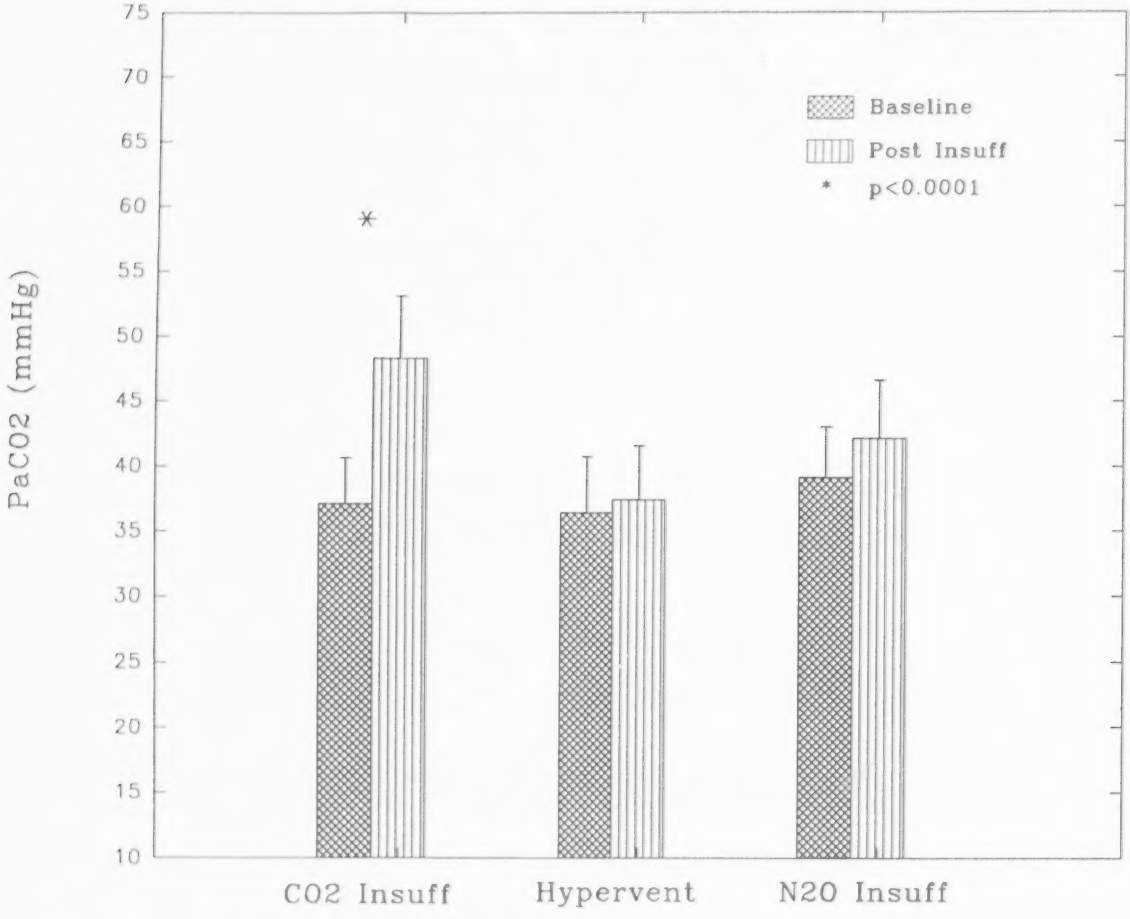
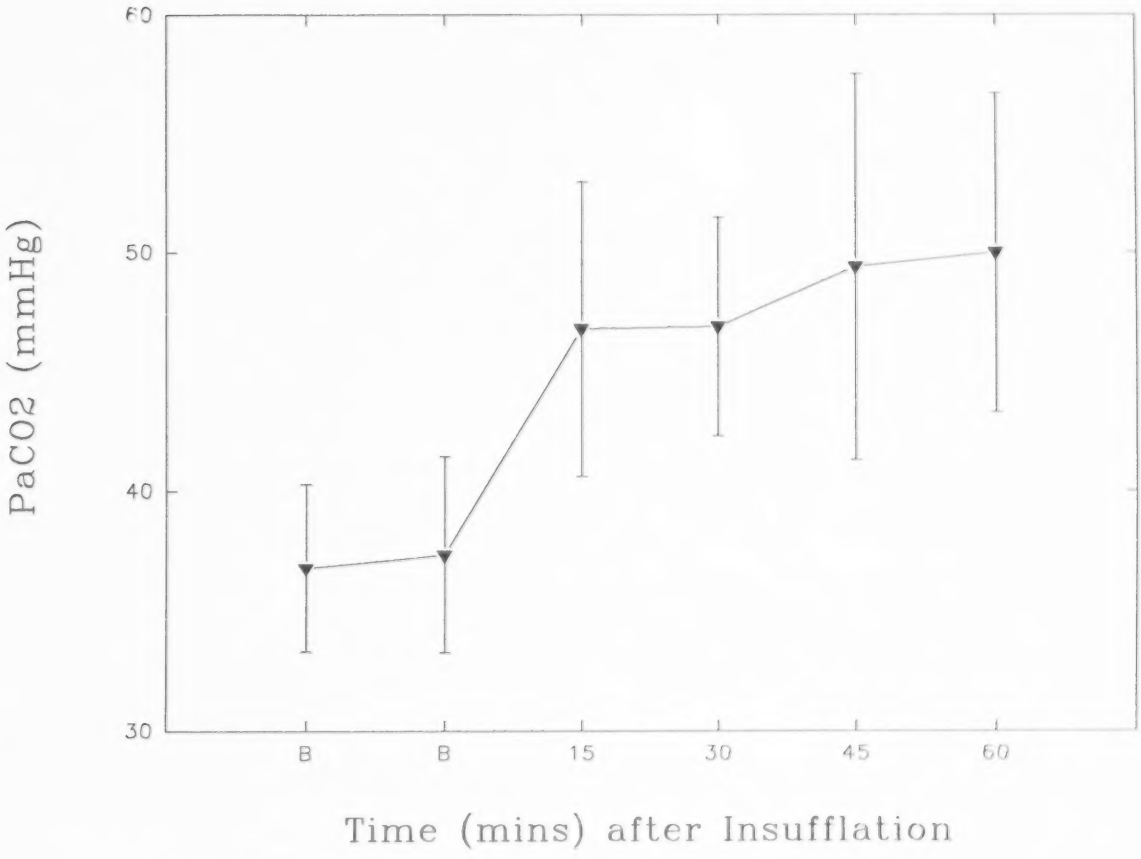


FIGURE 2

Time course analysis. $PaCO_2$ at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 3

Minute Ventilation at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

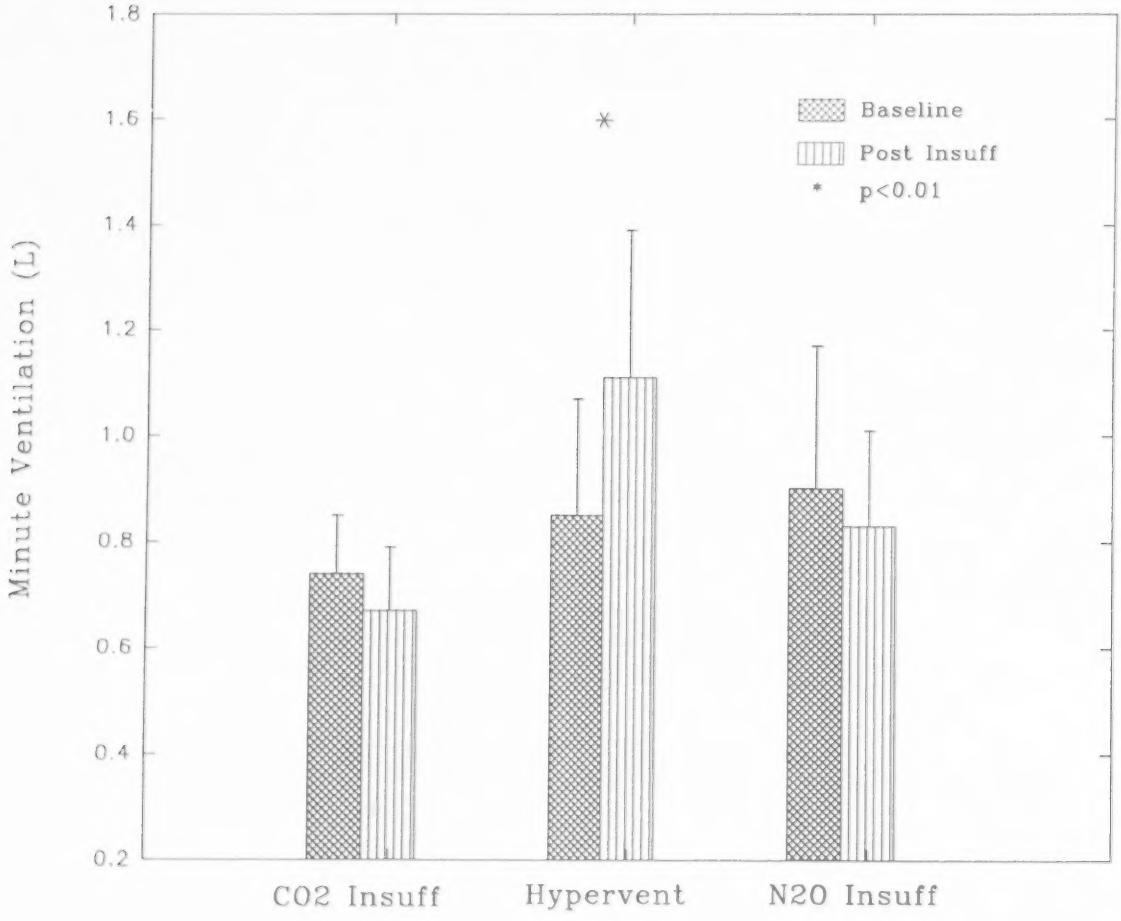
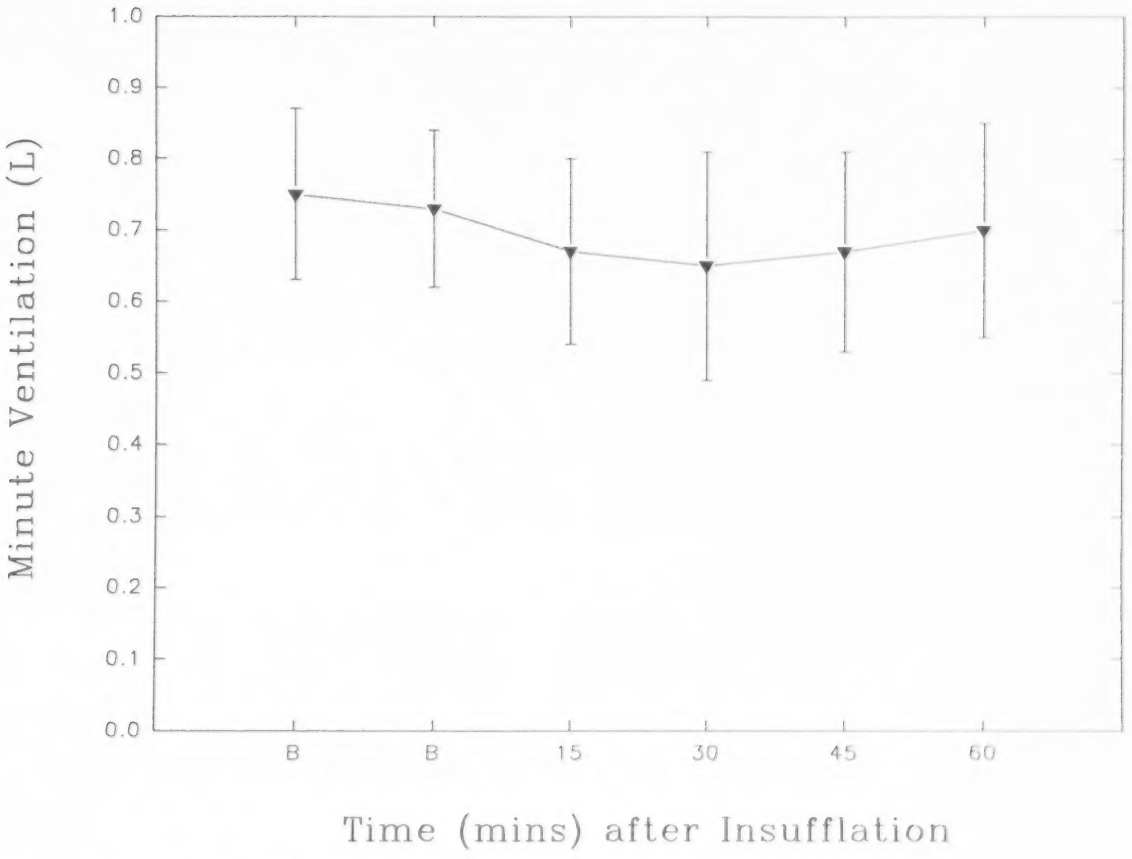


FIGURE 4

Time course analysis. Minute ventilation at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 5

PaO_2 at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

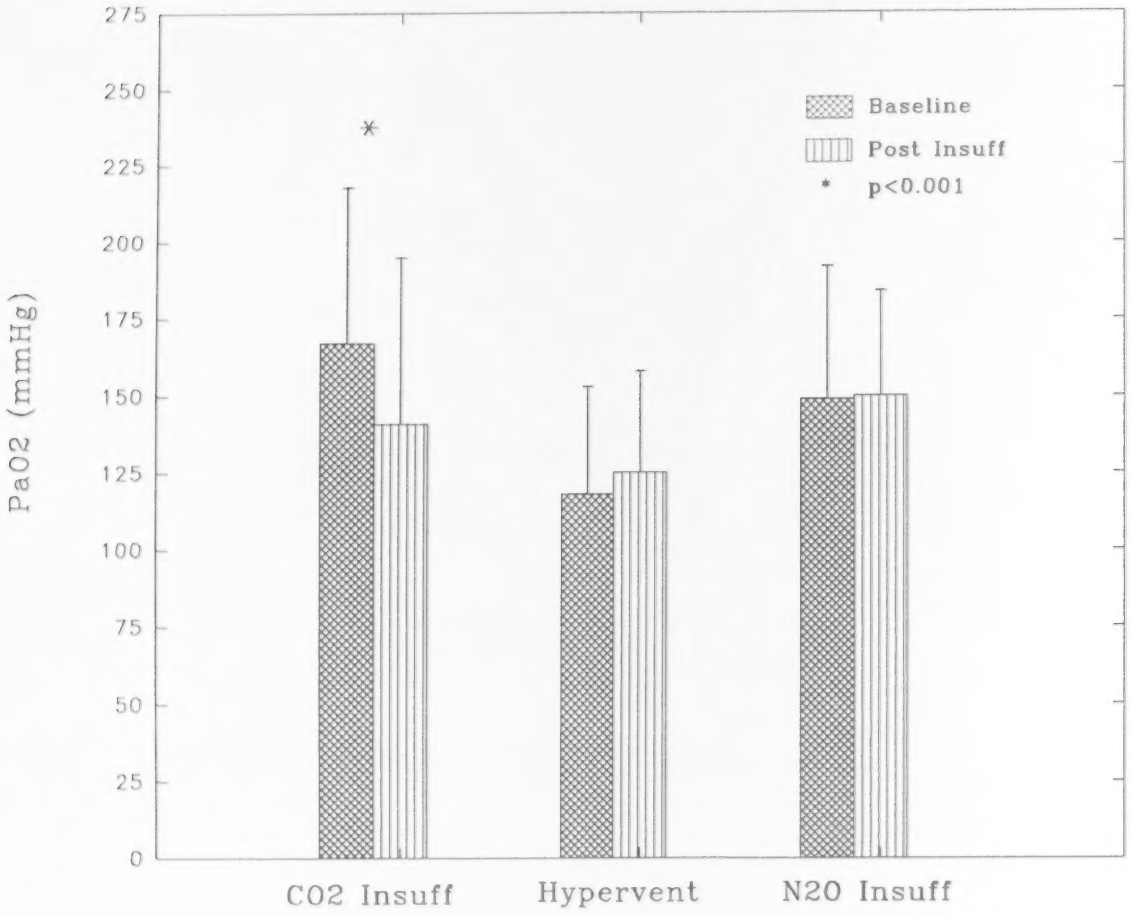


FIGURE 6

Mean systemic pressure at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

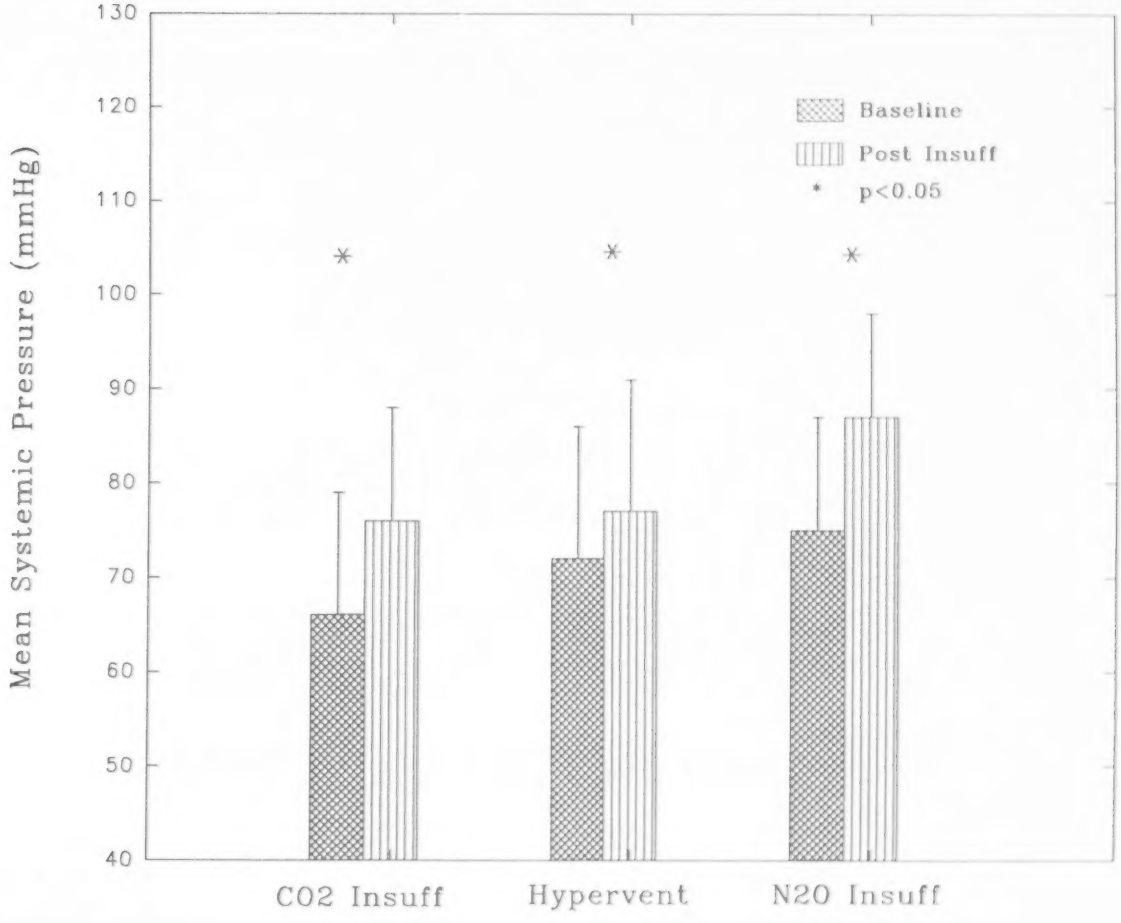
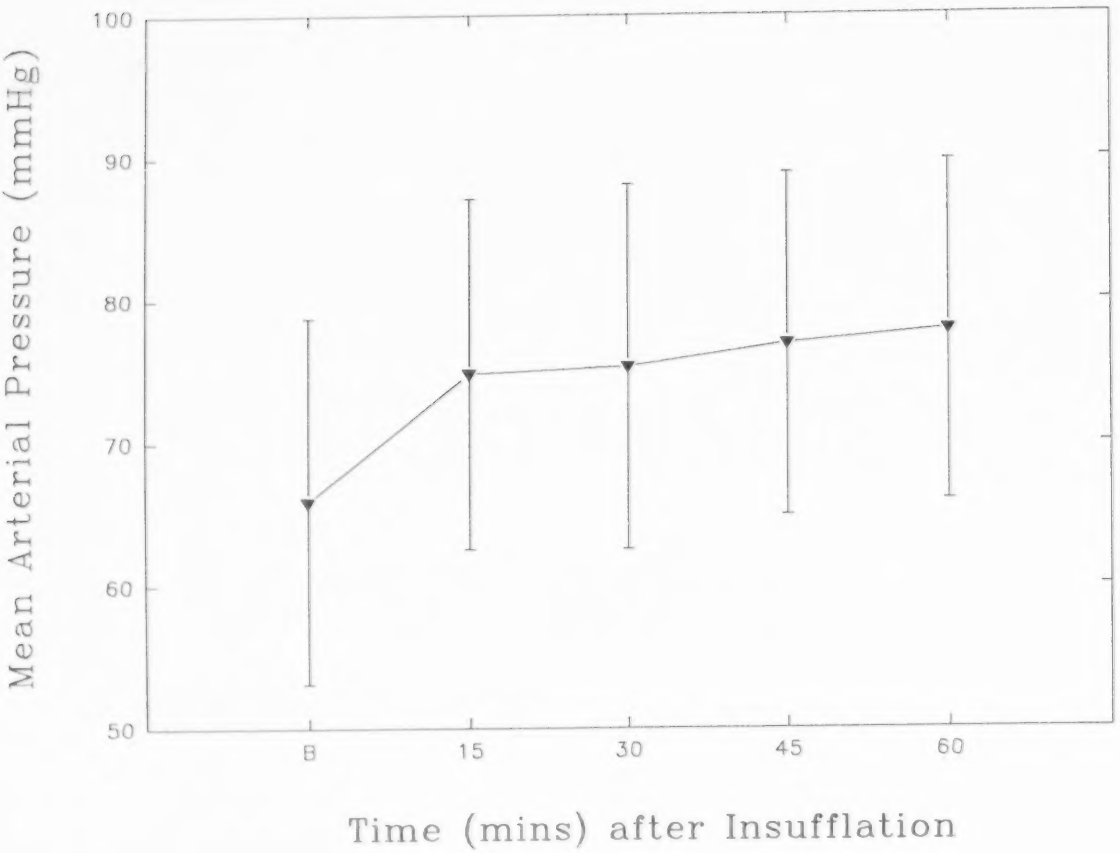


FIGURE 7

Time course analysis. Mean arterial pressure at baseline and during CO_2 insufflation alone.



B=baseline

FIGURE 8

Heart rate at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

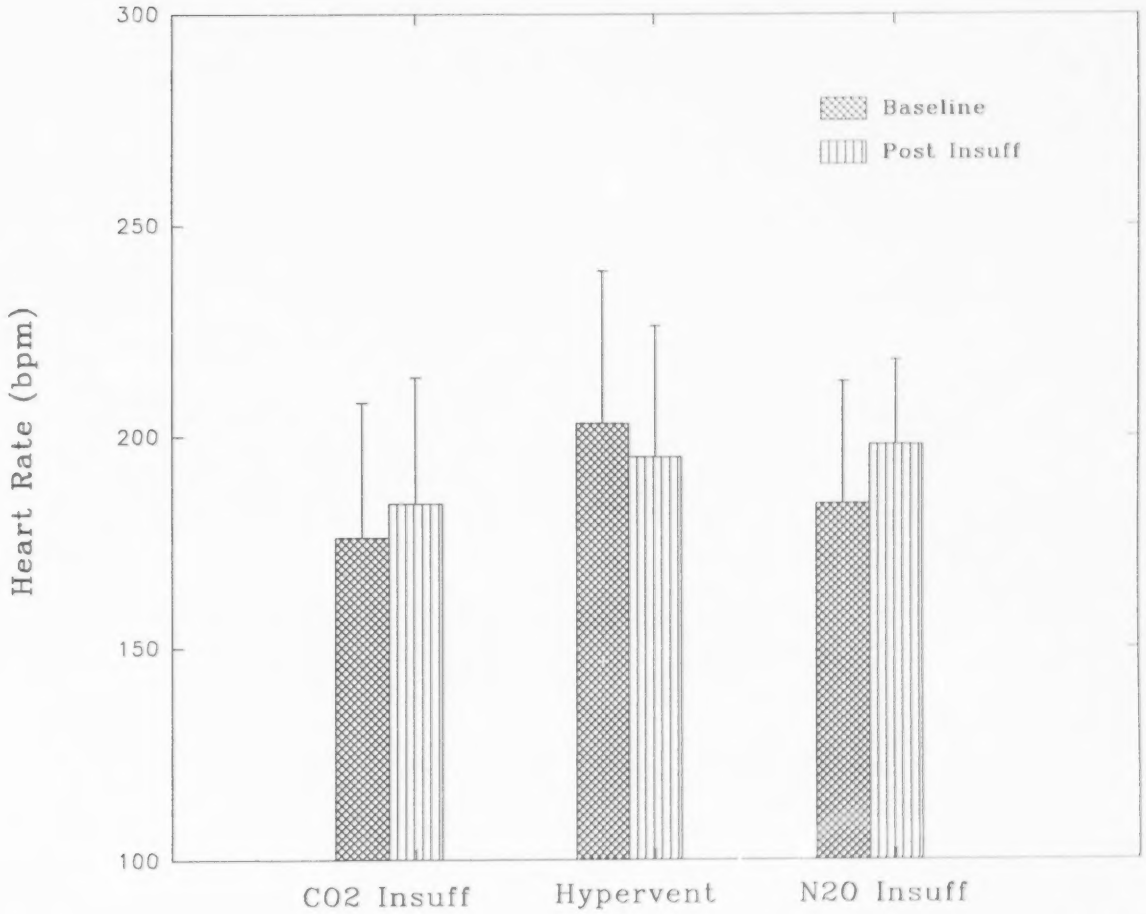
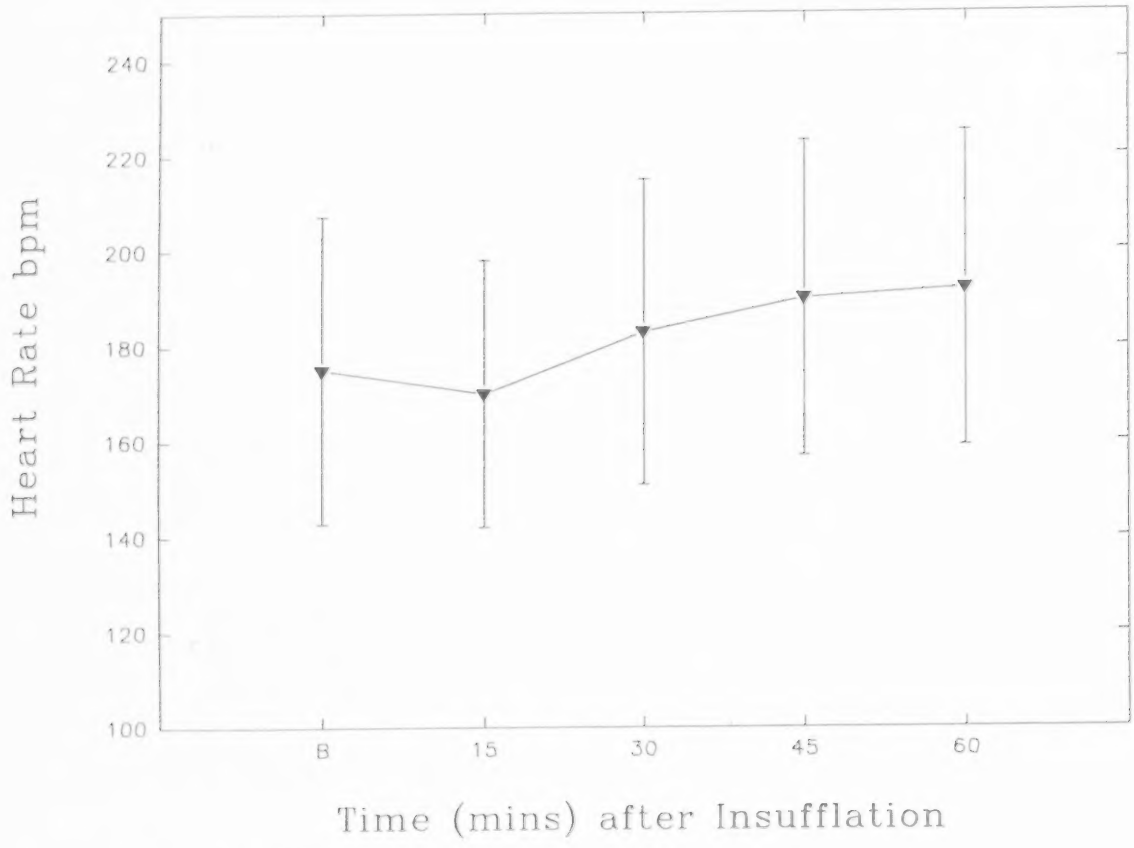


FIGURE 9

Time course analysis. Heart rate at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 10

Cardiac index at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

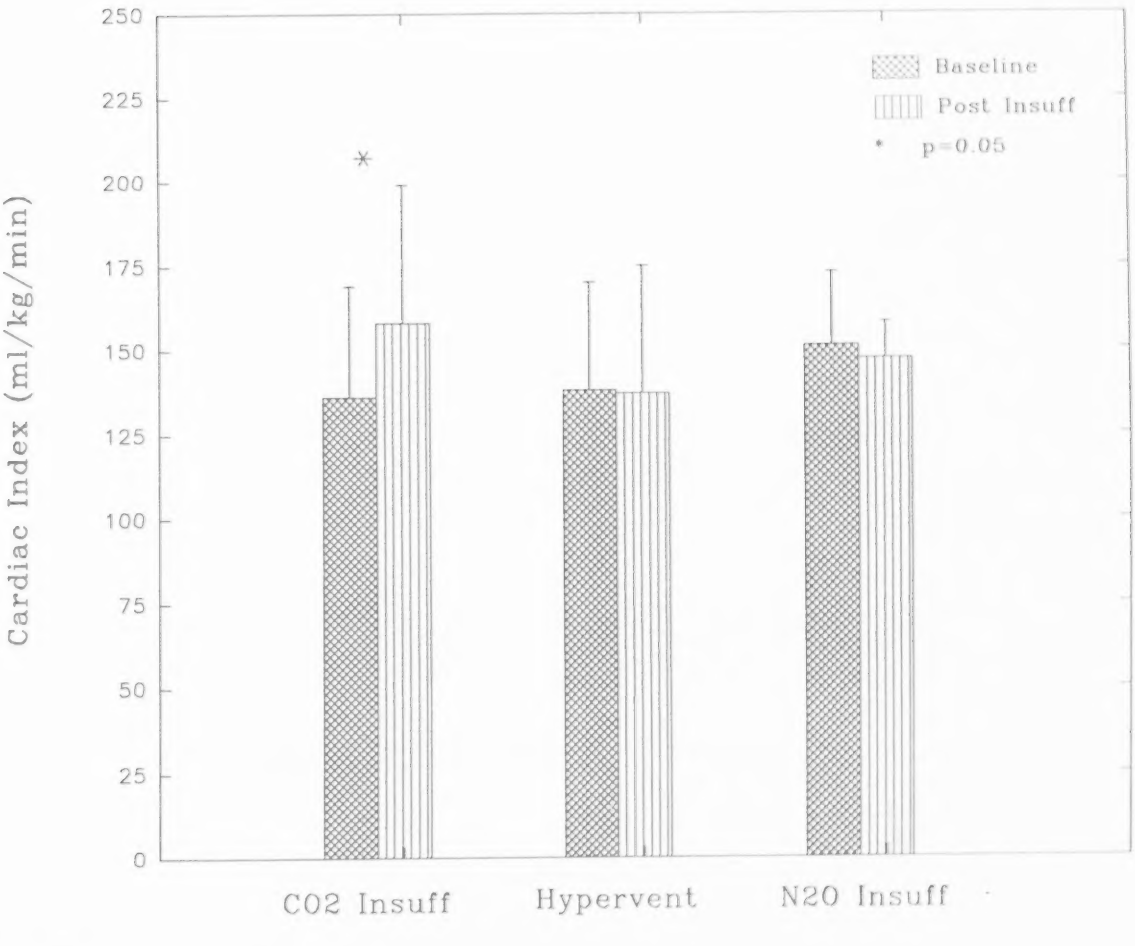
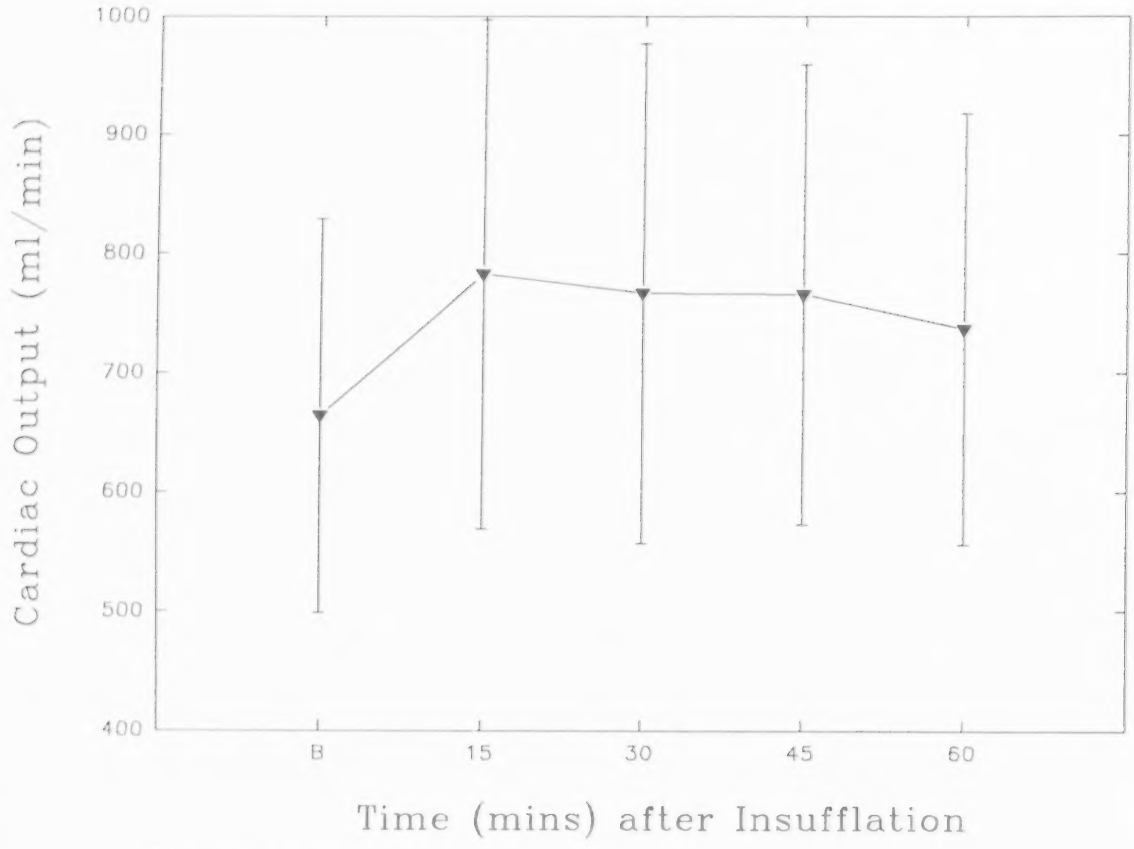


FIGURE 11

Time course analysis. Cardiac output at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 12

Central venous pressure at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

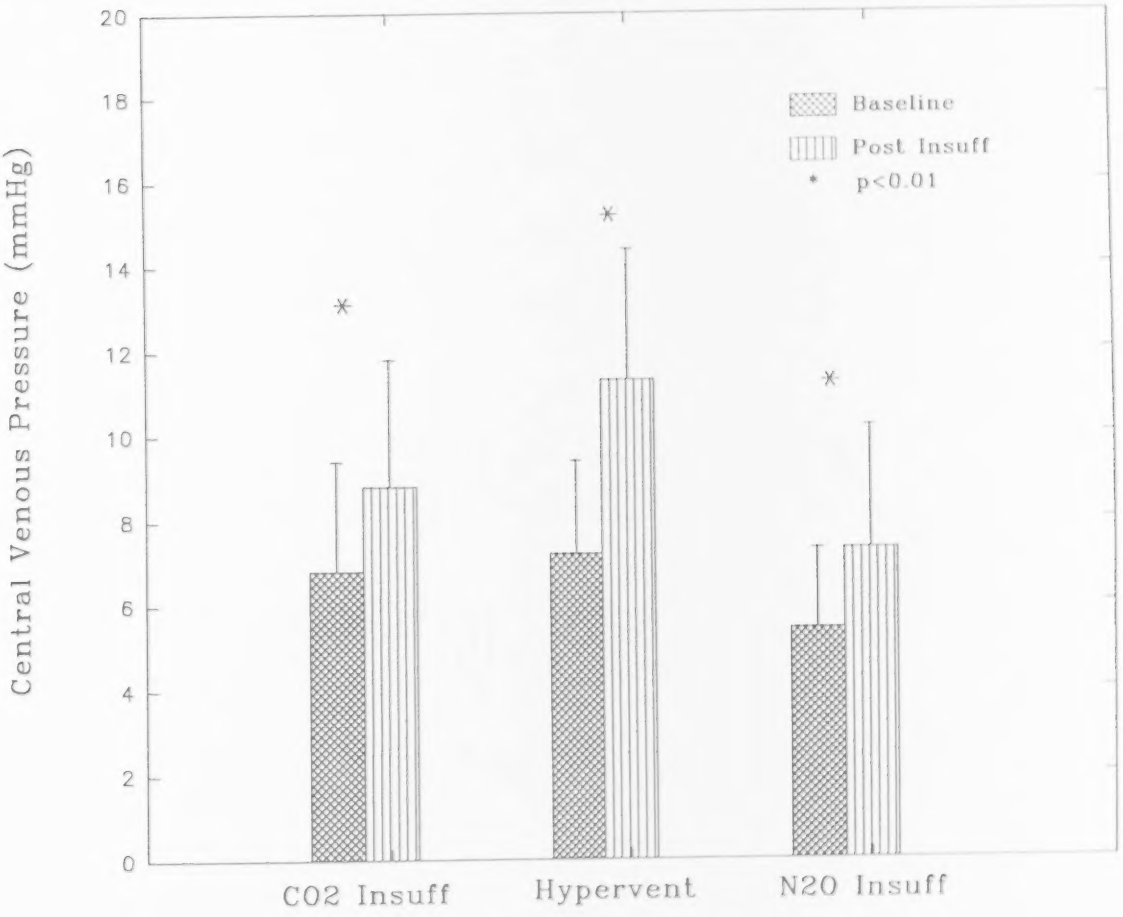
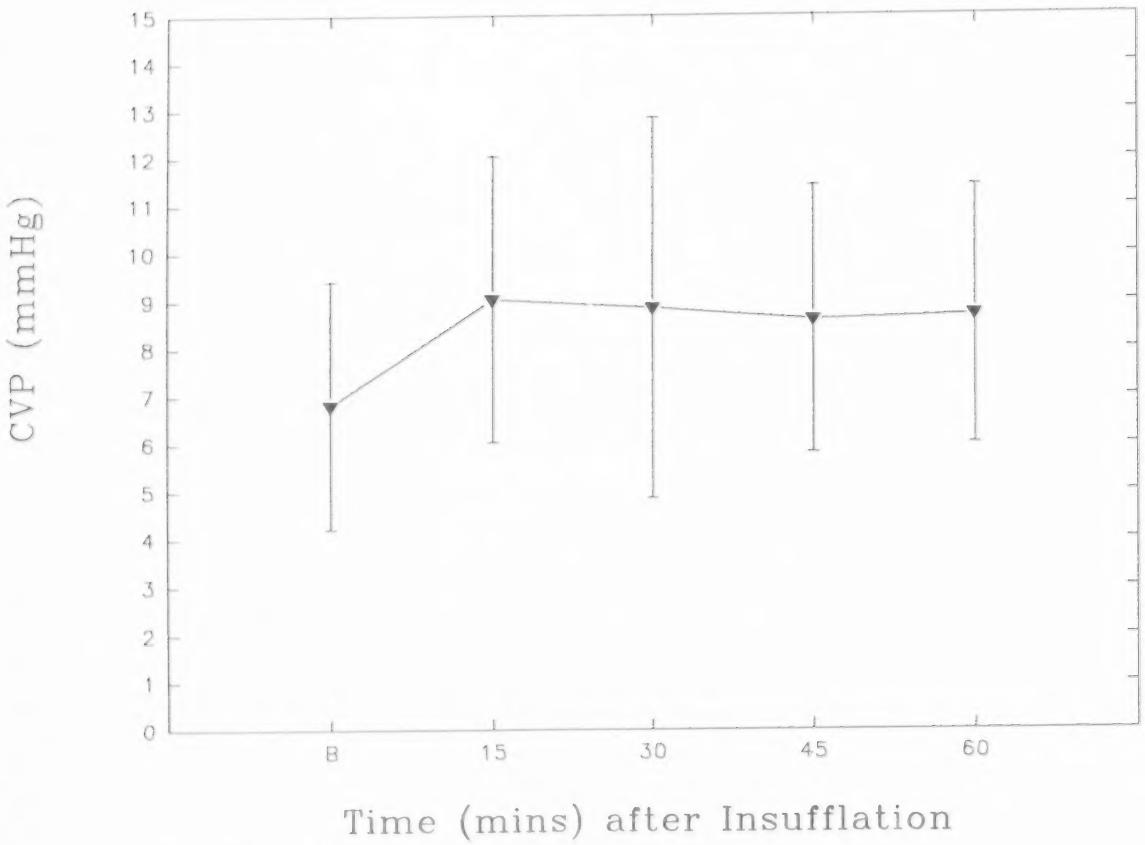


FIGURE 13

Time course analysis. Central venous pressure (CVP) at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 14

Inferior vena cava pressure at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

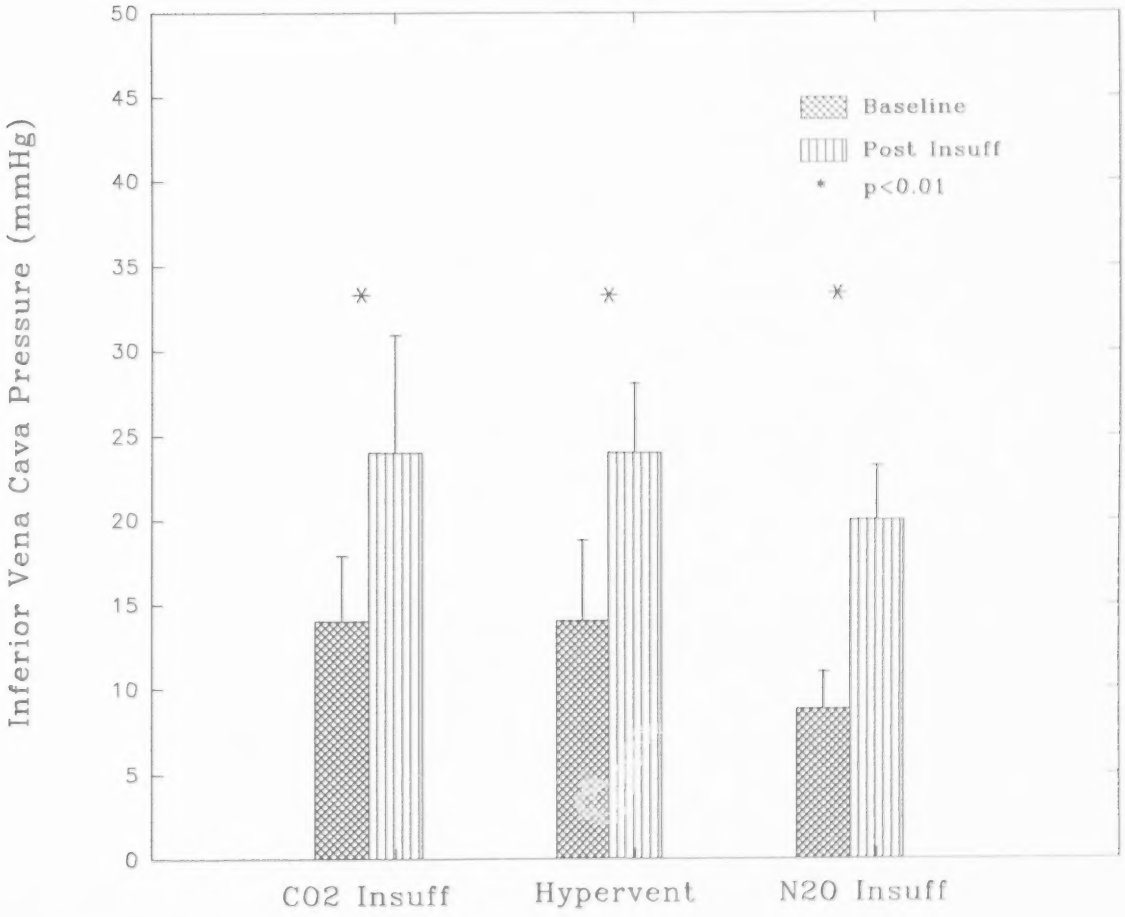
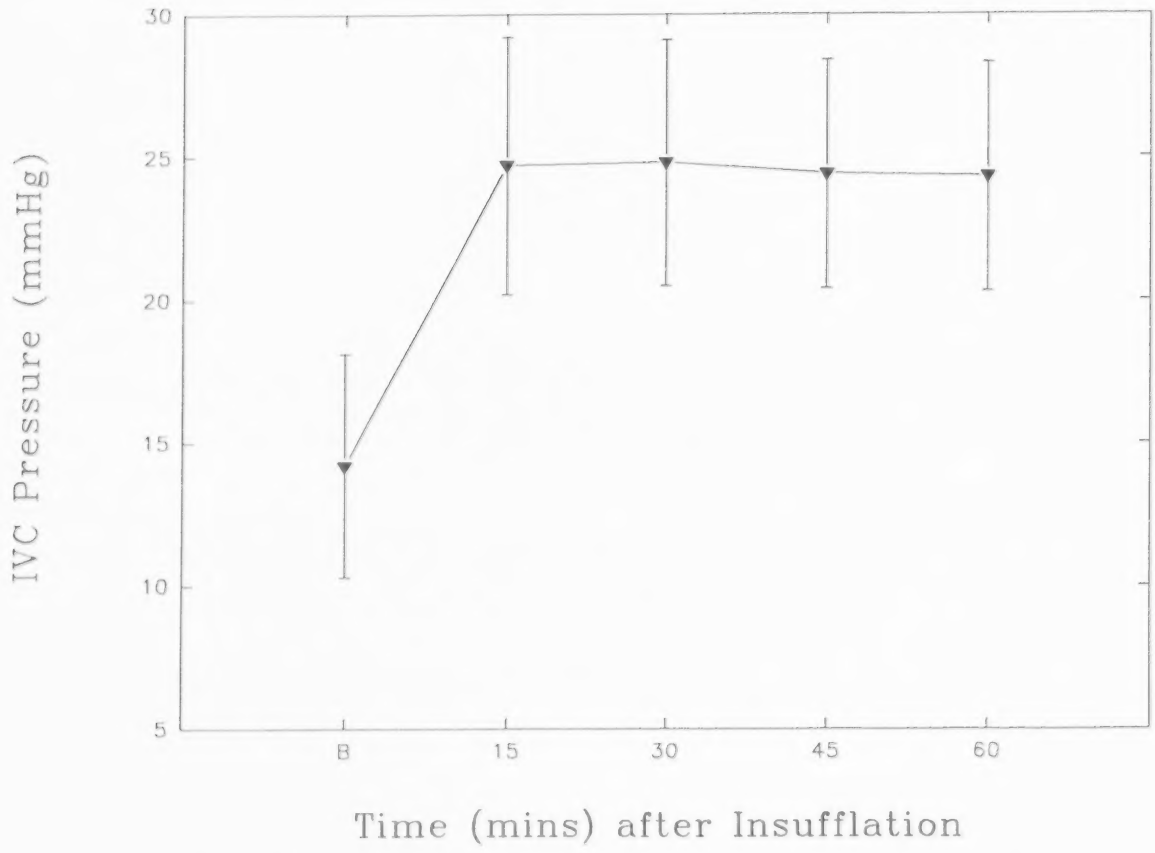


FIGURE 15

Time course analysis. Inferior vena cava pressure at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 16

Inferior vena cava flow (IVC flow) at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

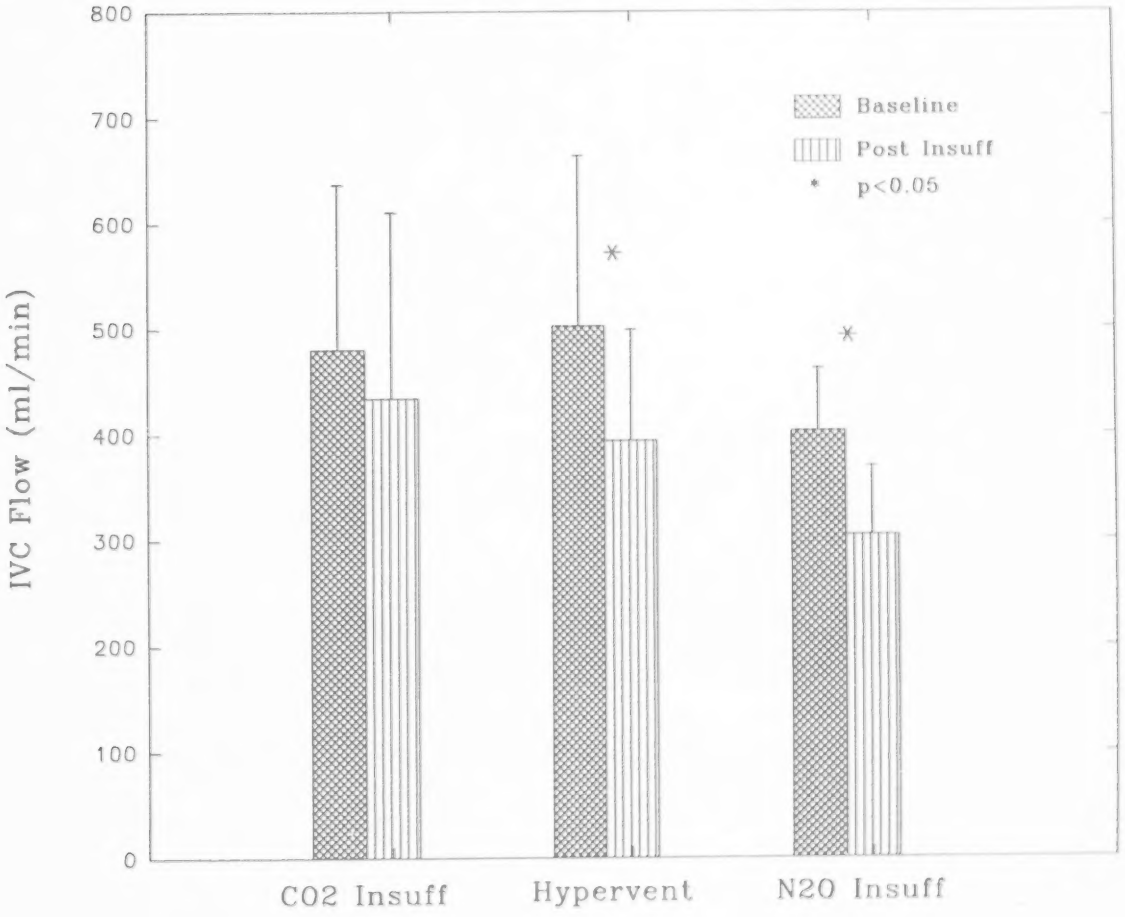
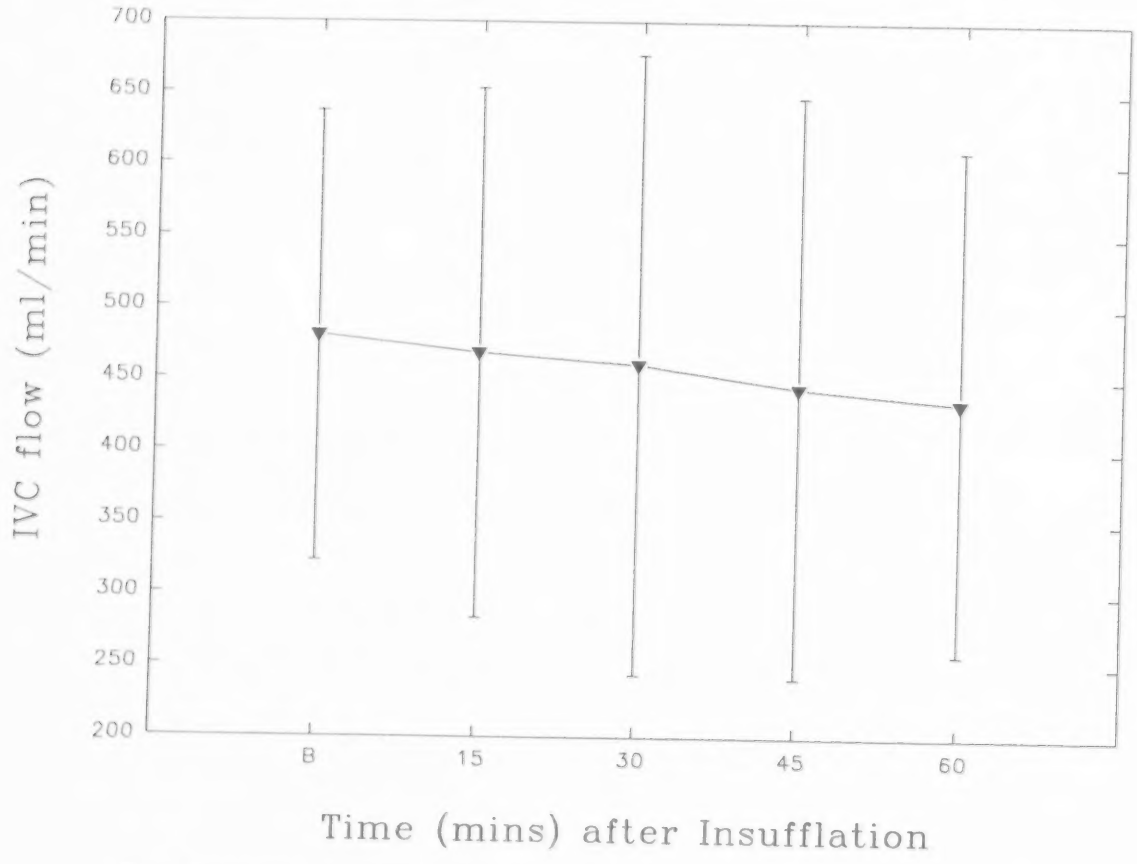


FIGURE 17

Time course analysis. Inferior vena cava flow (IVC Flow) at baseline and during CO_2 insufflation alone.



B = Baseline

FIGURE 18

Systemic vascular resistance at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

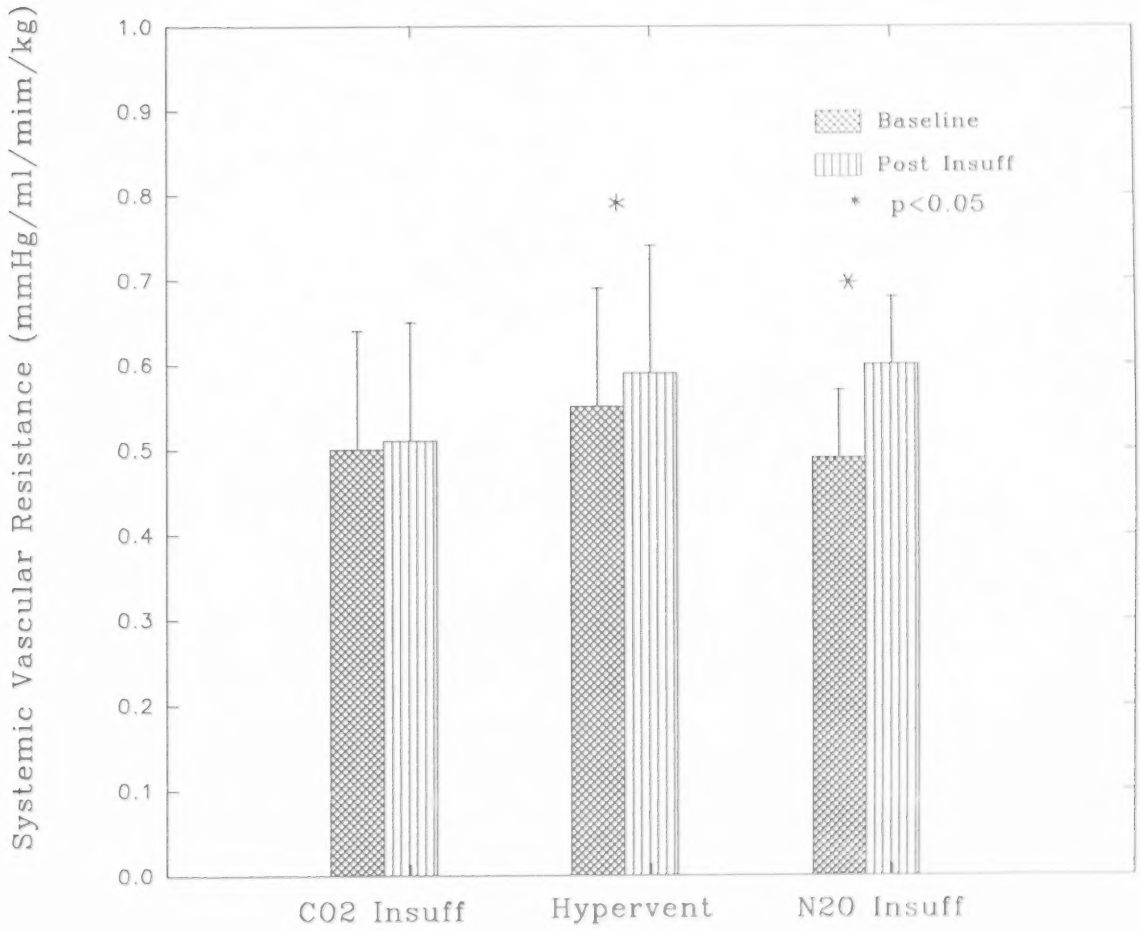


FIGURE 19

Mediastinal pressure at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

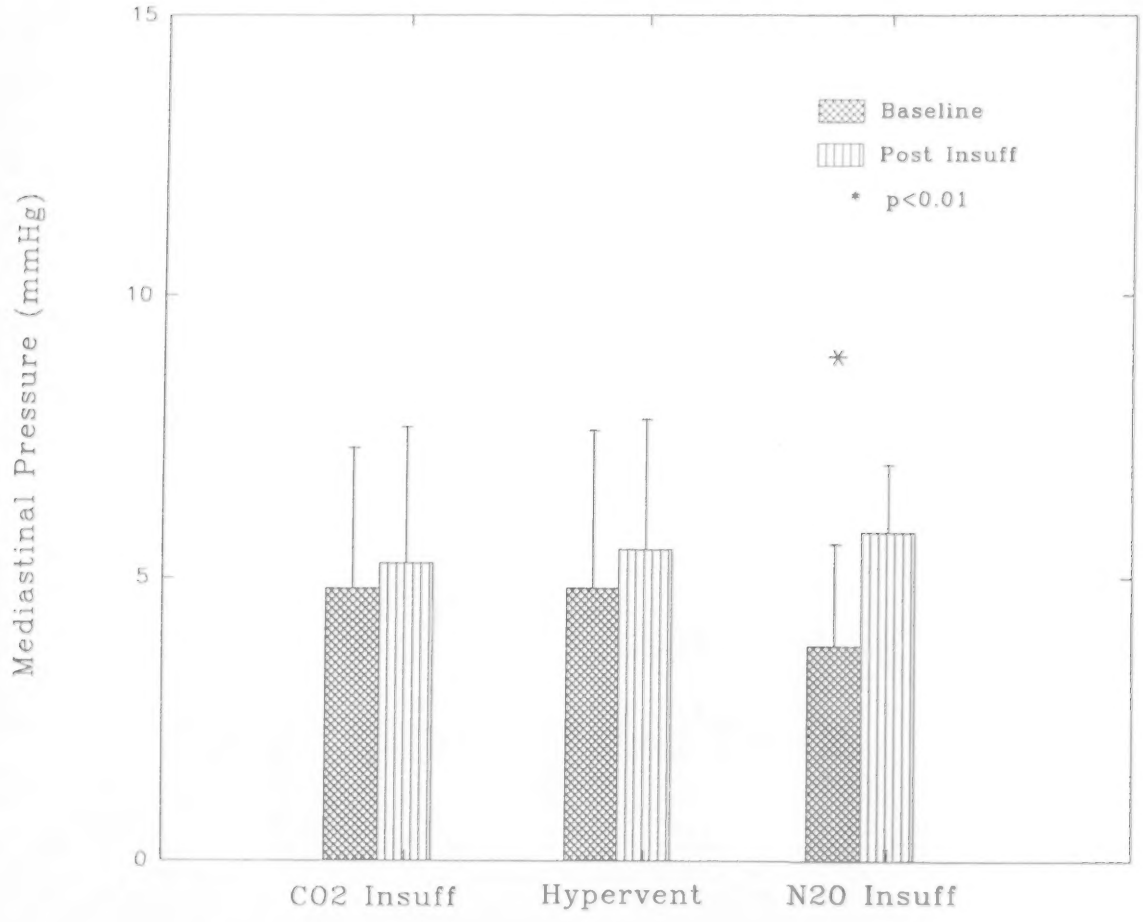


FIGURE 20

Femoral flow at baseline and post insufflation. Values shown are means ± SD. CO_2 insufflation alone (CO_2 Insuff), CO_2 insufflation with hyperventilation (Hypervent) and N_2O insufflation (N_2O Insuff).

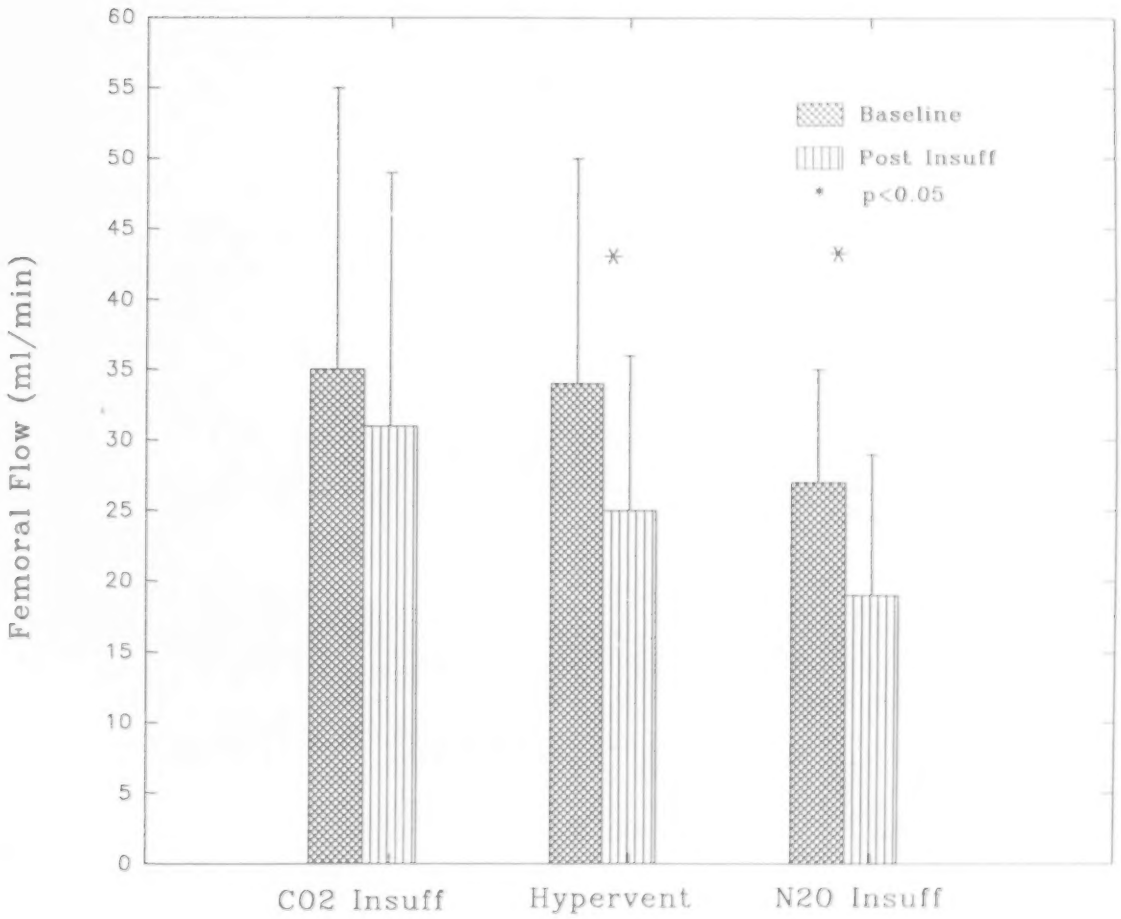
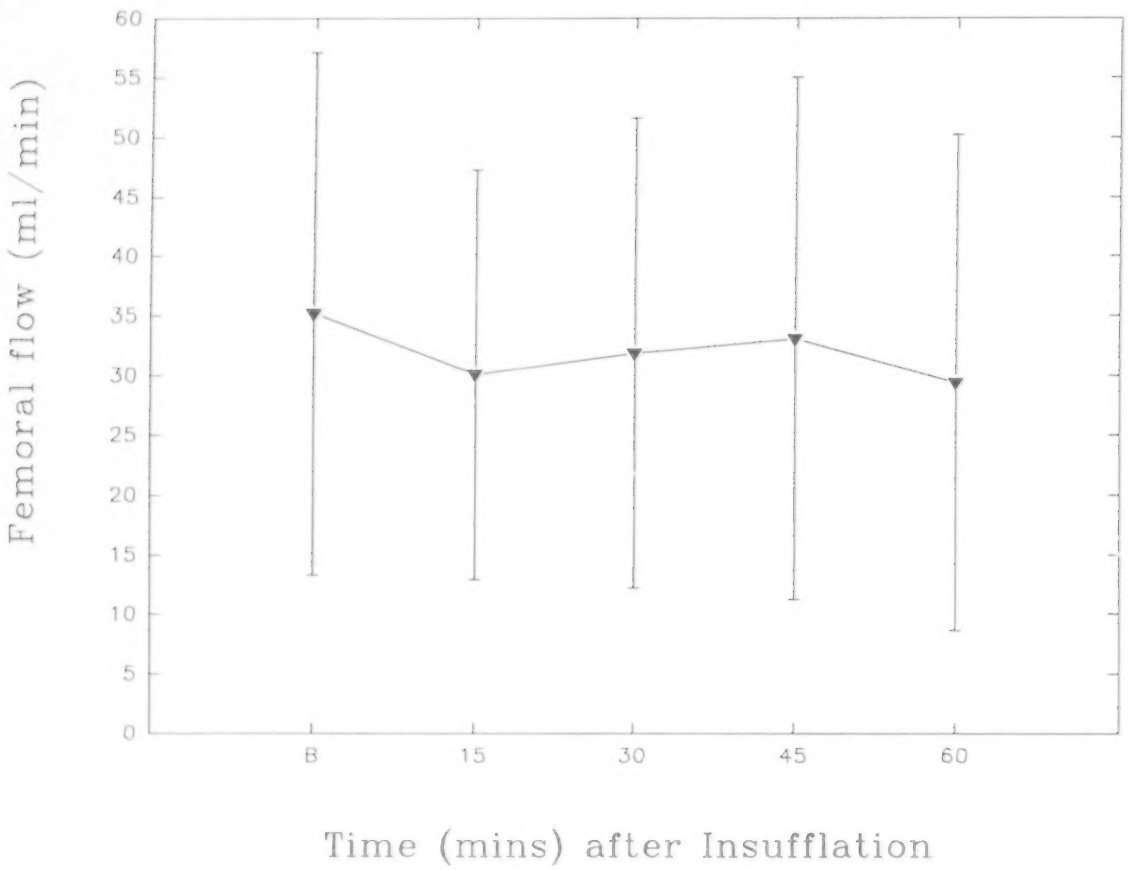


FIGURE 21

Time course analysis. Femoral flow at baseline and during CO_2 insufflation alone.



B = Baseline